



## REMARKS

Substitute specification is presented to correct minor errors in the specification as filed.

No new matter has been added.

In this regard:

1. On the change of "Trimethylene" at page 10, line 21 of the original specification, to --Optionally substituted trimethylene--:

(1) In view of passages "...the substituent being selected..." at page 10, line 23; "unsubstituted trimethylene..." at the same page, lines 24-25; and "those having one, two or more, preferably one or two substituents..." at the same page, lines 26-27, it would be evident for anyone skilled in the art that the groups such as trimethylene which are mentioned on the same page, lines 21-23, are unsubstituted or substituted, i.e., are optionally substituted.

(2) Also in view of a passage at page 166, last line to page 167, line 2, i.e. in Claim 1, which corresponds to page 10, lines 21-24, it would clearly be seen that-- Optionally substituted-- has been omitted from before "Trimethylene" at page 10, line 21.

(3) Furthermore, "Optionally substituted trimethylene..." is correctly mentioned in the original Japanese language PCT application, page 10, line 18.

2. On the addition of--at the same temperature-- after "stirring" at page 65, line 14 of the original specification:

The passage at page 56, line 27 of the original Japanese language PCT application which corresponds to the U.S. specification, page 65, line 14, is correctly written, including "at the same temperature". Hence, the above-captioned change is a correction of an obvious error which occurred during the English translation of the PCT specification.


3. On the addition of--under reduced pressure-- after "solvent off" at page 74, line 26 of the original specification:

Support is similar to that in above paragraph 2. The corresponding passage (page 67, line 3) in the original PCT application is correctly written.

Favorable action is now requested.

Respectfully submitted,

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November 18, 2003



## DESCRIPTION

RECEIVED  
NOV 21 2003  
TECH CENTER 1600/2900

### NOVEL AMIDE DERIVATIVES

#### 5 Technical Field

This invention relates to novel amide derivatives, processes for preparing them, pharmaceuticals containing them and their use as medicines, especially in the treatment of various diseases of the respiratory, urinary and digestive systems.

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#### Background Art

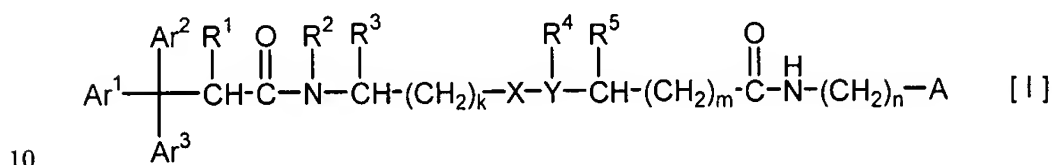
Antagonism to muscarinic receptors are known to cause bronchodilation, gastrointestinal hypanakinesis, gastric hyposecretion, dry mouth, mydriasis, suppression of bladder  
15 contraction, hypohidrosis, tachycardia and the like [cf. Basic and Clinical Pharmacology, 4th ed., APPLETON & LANGE, pp. 83-92 (1989) and Drug News & Perspective, 5(6), pp. 345-352 (1992)].

It has recently been made clear that there are at least three subtypes of muscarinic receptors; M<sub>1</sub> receptors being present  
20 mainly in the brain; M<sub>2</sub> receptors, mainly in the heart, and M<sub>3</sub> receptors, on smooth muscles and glandular tissues. Whereas, all of the large number of compounds heretofore known to exhibit antagonism to muscarinic receptors non-selectively antagonize the three subtypes of muscarinic receptors. Consequently, attempts to  
25 use ~~these compounds~~ these compounds as therapeutic or prophylactic agents for diseases of the respiratory system have caused undesirable side effects such as dry mouth, nausea and mydriasis. Still in addition, particularly serious side effects associated with the central nervous system, such as dementia, attributable to M<sub>1</sub> receptors and  
30 those associated with the heart, such as tachycardia mediated by M<sub>2</sub> receptors pose problems and their solution has been strongly in demand.

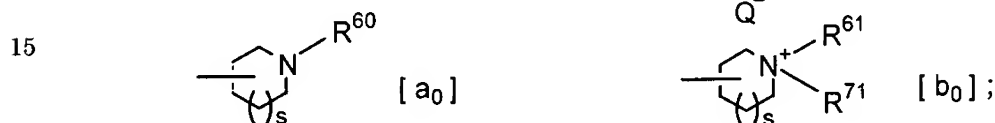
## Disclosure of the Invention

An object of the present invention is to provide treating agents of diseases associated with muscarinic M<sub>3</sub> receptors, said agents exhibiting highly selective antagonism to muscarinic M<sub>3</sub> receptors and little side effects, and being safe and effective.

We have discovered that ~~these compounds~~ those compounds which are represented by the following general formula [I]



[in which A stands for a group of the following formula [a<sub>0</sub>] or [b<sub>0</sub>]



Ar<sup>1</sup>, Ar<sup>2</sup> and Ar<sup>3</sup> each independently stands for optionally substituted phenyl, the substituent being selected from the group consisting of halogen, hydroxyl, lower alkyl, lower alkenyl, lower alkoxy, carbamoyl, lower alkylcarbamoyl and di-lower alkylcarbamoyl; k means 0 or 1; m, n and s each independently means 0, 1 or 2; R<sup>1</sup> stands for hydrogen or optionally substituted lower alkyl, the substituent being selected from the group consisting of hydroxyl, amino, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl and imidazolyl; R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> each independently stands for hydrogen or optionally substituted lower alkyl, the substituent being selected from the group consisting of



hydroxyl, amino, carbamoyl, lower alkylcarbamoyl, di-lower  
 alkylcarbamoyl and imidazolyl, or R<sup>2</sup> and R<sup>3</sup>, or R<sup>4</sup> and R<sup>5</sup>,  
 may together stand for, independently of each other,  
 optionally substituted trimethylene, propenylene,  
 5 tetramethylene or 2-butenylene group, the substituent being  
 selected from the group consisting of oxo, hydroxyl, amino,  
 lower alkoxy, lower alkanoyloxy, lower alkylamino, di-lower  
 alkylamino, (imino-lower alkyl)amino, lower alkanoylamino,  
 lower alkoxycarbonylamino, (lower alkylcarbamoyl)amino,  
 10 lower alkylsulfonylamino, guanidino, lower alkoxycarbonyl,  
 carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl,  
 imidazolyl and a group represented by -R<sup>7</sup>, R<sup>7</sup> standing for  
 optionally substituted lower alkyl, the substituent being  
 selected from the group consisting of hydroxyl, amino,  
 15 carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl,  
 lower alkoxycarbonyl and imidazolyl; R<sup>60</sup> stands for hydrogen,  
 C<sub>1</sub>-C<sub>10</sub> alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl  
 whose ring portion may be substituted with lower alkyl,  
 cycloalkenyl-lower alkyl or aralkyl; R<sup>61</sup> and R<sup>71</sup> each  
 20 independently stands for C<sub>1</sub>-C<sub>10</sub> alkyl, lower alkenyl,  
 cycloalkyl, cycloalkyl-lower alkyl whose ring portion may be  
 substituted with lower alkyl, cycloalkenyl-lower alkyl or  
 aralkyl, or R<sup>61</sup> and R<sup>71</sup> may together stand for optionally  
 substituted trimethylene, tetramethylene, 2-butenylene,  
 25 pentamethylene, 3-oxapentamethylene or 2, 3-epoxytetra-  
 methylene group, the substituent being selected from the  
 group consisting of oxo, hydroxyl, lower alkyl and lower  
 alkoxy; X stands for carbonyl or methylene; Y stands for  
 nitrogen or methine; and Q<sup>-</sup> stands for anion]  
 30 exhibit highly selective antagonism to muscarinic M<sub>3</sub> receptors, little  
 side effect and high safety, and are very useful for treating various  
 diseases which are associated with muscarinic M<sub>3</sub> receptors, eg., such  
 respiratory diseases as chronic obstructive pulmonary diseases,

chronic bronchitis, asthma, chronic respiratory tract obstruction, fibroid lung, pulmonary emphysema and rhinitis; digestive diseases such as irritable bowel syndrome, convulsive colitis, gastroduodenal ulcer, convulsion or hyperanakisia of digestive tract, diverticulitis  
5 and pain accompanying contraction of smooth muscles of the digestive system; urinary diseases accompanied by dysuria like urinary incontinence, urgency and pollakiuria in nervous pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis; and motion sickness; and have completed the  
10 present invention.

The present invention relates to the compounds represented by above general formula [I] or salts thereof, processes for their preparation and their use.

~~Hereafter the~~ Hereafter the invention is explained in further  
15 details, in which the terms used mean the following.

“Halogen” means fluorine, chlorine, bromine and iodine atoms.

“Lower alkyl” means C<sub>1</sub>-C<sub>6</sub> linear or branched alkyl groups, examples of which include methyl, ethyl, propyl, isopropyl, butyl,  
20 isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl and isohexyl groups.

“Lower alkenyl” means C<sub>2</sub>-C<sub>6</sub> linear or branched alkenyl groups, examples of which include vinyl, 1-propenyl, 2-propenyl, isopropenyl, 3-butenyl, 2-butenyl, 1-butenyl, 1-methyl-2-propenyl,  
25 1-methyl-1-propenyl, 1-ethyl-1-ethenyl, 2-methyl-2-propenyl, 2-methyl-1-propenyl, 3-methyl-2-butenyl and 4-pentenyl groups.

“Lower alkoxy” means C<sub>1</sub>-C<sub>6</sub> linear or branched alkoxy groups, examples of which include methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, isobutoxy, tert-butoxy, pentyloxy,  
30 isopentyloxy, hexyloxy and isohexyloxy groups.

“Lower alkylcarbamoyl” means carbamoyl groups which are mono-substituted with said lower alkyl groups, examples of which include methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl,

isopropylcarbamoyl, butylcarbamoyl, sec-butylcarbamoyl and tert-butylcarbamoyl groups.

“Di-lower alkylcarbamoyl” means carbamoyl groups which are di-substituted with said lower alkyl groups, examples of which  
5 include dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, dipropylcarbamoyl, methylpropylcarbamoyl and di-isopropylcarbamoyl groups.

“Lower alkylamino” means amino groups which are mono-substituted with said lower alkyl groups, examples of which  
10 include methylamino, ethylamino, propylamino, isopropylamino, butylamino, sec-butylamino and tert-butylamino groups.

“Di-lower alkylamino” means amino groups which are di-substituted with said lower alkyl groups, examples of which include dimethylamino, diethylamino, ethylmethylamino,  
15 dipropylamino, methylpropylamino and di-isopropylamino groups.

“Imino-lower alkyl” means said lower alkyl groups which are mono-substituted with imino group, examples of which include formimidoyl, acetimidoyl, propanimidoyl, butanimidoyl, pentanimidoyl and hexanimidoyl groups.

20 “(Imino-lower alkyl) amino” means amino groups which are mono-substituted with said imino-lower alkyl groups, examples of which include formimidoylamino, acetimidoylamino, propanimidoylamino, butanimidoylamino, pentanimidoylamino and hexanimidoylamino groups.

25 “Lower alkanoyl” means C<sub>1</sub>-C<sub>6</sub> linear or branched alkanoyl groups, examples of which include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl and pivaloyl groups.

“Lower alkanoyloxy” means alkanoyloxy groups having said lower alkanoyl groups, examples of which include acetoxy,  
30 propionyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy and pivaloyloxy groups.

“Lower alkanoylamino” means amino groups which are mono-substituted with said lower alkanoyl groups, examples of which

include formylamino, acetylamino, propionylamino, butyrylamino, isobutyrylamino, valerylamino, isovalerylamino and pivaloylamino groups.

“(Lower alkylcarbamoyl) amino” means amino groups which  
5 are mono-substituted with said lower alkylcarbamoyl groups, examples of which include (methylcarbamoyl) amino, (ethylcarbamoyl)amino, (propylcarbamoyl)amino, (isopropylcarbamoyl)amino, (butylcarbamoyl)amino, (sec-butylcarbamoyl)amino and (tert-butylcarbamoyl)amino groups.

10 “Lower alkylsulfonyl” means alkylsulfonyl groups having said lower alkyl groups, examples of which include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, sec-butylsulfonyl and tert-butylsulfonyl groups.

“Lower alkylsulfonylamino” means amino groups which are  
15 mono-substituted with said lower alkylsulfonyl groups, examples of which include methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, isopropylsulfonylamino, butylsulfonylamino, sec-butylsulfonylamino and tert-butylsulfonylamino groups.

“Lower alkoxy carbonyl” means alkoxy carbonyl groups  
20 having said lower alkoxy groups, examples of which include methoxy carbonyl, ethoxy carbonyl, propoxy carbonyl, isopropoxy carbonyl, butoxy carbonyl, isobutoxy carbonyl, tert-butoxy carbonyl and pentyloxy carbonyl groups.

“Lower alkoxy carbonylamino” means amino groups which  
25 are mono-substituted with said lower alkoxy carbonyl groups, examples of which include methoxy carbonylamino, ethoxy carbonylamino, propoxy carbonylamino, isopropoxy carbonylamino, butoxy carbonylamino, isobutoxy carbonylamino, tert-butoxy carbonylamino and pentyloxy carbonylamino groups.

30 “C<sub>1</sub>-C<sub>10</sub> alkyl” means C<sub>1</sub>-C<sub>10</sub> linear or branched alkyl groups, examples of which includes, besides those earlier exemplified lower alkyl groups, 2-methylbutyl, 2-ethylbutyl, 2-methylpentyl, heptyl, octyl, nonyl and decyl groups.

“Cycloalkyl” means C<sub>3</sub>-C<sub>10</sub> cycloalkyl groups, examples of which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl groups.

“Cycloalkyl-lower alkyl” means said lower alkyl groups  
5 having above cycloalkyl groups, examples of which include cyclopropylmethyl, 2-cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 1-cyclopentylethyl, 2-cyclopentylethyl, cyclohexylmethyl, 1-cyclohexylethyl, 2-cyclohexylethyl, cycloheptylmethyl and cyclooctylmethyl groups.

10 “Cycloalkyl-lower alkyl whose ring portion may be substituted with lower alkyl” means either above cycloalkyl-lower alkyl groups or said cycloalkyl-lower alkyl groups having one, two or more, preferably one or two same or different, earlier named lower alkyl groups at the optional, substitutable position or positions on the  
15 cycloalkyl group, examples of which include, besides above-exemplified cycloalkyl-lower alkyl groups, 1-(1-methylcyclopropyl)-ethyl, 2-(1-methylcyclopropyl)ethyl, (2,2-dimethylcyclopentyl)methyl, 1-(2,2-dimethylcyclopentyl)ethyl and 2-(2,2-dimethylcyclopentyl)ethyl groups.

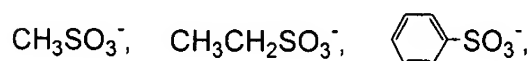
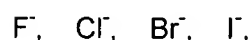
20 “Cycloalkenyl” means C<sub>3</sub>-C<sub>10</sub> cycloalkenyl groups, examples of which include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl and cyclodecenyl groups.

“Cycloalkenyl-lower alkyl” means said lower alkyl groups  
25 having said cycloalkenyl groups, examples of which include cyclopropenylmethyl, cyclobutenylmethyl, cyclopentenylmethyl, cyclohexenylmethyl, cycloheptenylmethyl, cyclooctenylmethyl, cyclononenylmethyl and cyclodecenylmethyl groups.

“Aralkyl” means said lower alkyl groups having aryl groups  
30 such as phenyl, naphthyl or anthryl, examples of which include benzyl, 1-phenylethyl, 2-phenylethyl, 1-naphthylmethyl and 2-naphthylmethyl groups.

“Anion” means those forming a pair with ammonium ions on

the compounds of the present invention, which electrically neutralize said compounds. While they are not subject to particular limitations so long as they are pharmaceutically acceptable, anions formed from halogen atoms, inorganic acids, organic sulfonic acids, carboxylic  
5 acids and the like, such as



may be named as examples.

10 "Salts" of the compounds represented by the general formula [I] means, for example, those pharmaceutically acceptable and customarily used salts of the compounds whose A is expressed by the formula [a<sub>0</sub>], referring to the general formula [I]. As examples of such salts, acid addition salts at the positions of basic nitrogen atom  
15 may be named.

Examples of the acid addition salts include inorganic acid salts such as hydrochloride, sulfate, nitrate, phosphate and perchlorate; organic acid salts such as maleate, fumarate, tartarate, citrate, ascorbate and trifluoroacetate; and sulfonic acid salts such as  
20 methanesulfonate, isethionate, benzenesulfonate and p-toluene-sulfonate.

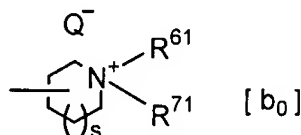
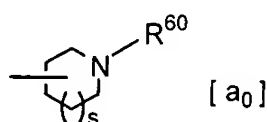
"Treating agent" means medicines which are used for treatment and/or prophylaxis of various diseases.

The compounds of the present invention in occasions have  
25 stereoisomers such as optical isomers, diastereoisomers or geometrical isomers, depending on the form of the substituents therein. The compounds of the present invention cover all of those

stereoisomers and their mixtures.

For more specific disclosures of the compounds of the present invention which are represented by the general formula [I], the symbols used in said formula [I] are explained in further details in the following, citing their preferred specific examples.

A stands for a group of the following formula [a<sub>0</sub>] or [b<sub>0</sub>]:



R<sup>60</sup> stands for hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl whose ring portion may be substituted with lower alkyl, cycloalkenyl-lower alkyl or aralkyl.

Examples of C<sub>1</sub>-C<sub>10</sub> alkyl groups as R<sup>60</sup> include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl, heptyl, octyl and decyl.

Preferred examples of lower alkenyl group as R<sup>60</sup> include 2-propenyl and 3-butenyl.

Preferred examples of cycloalkyl group as R<sup>60</sup> include cyclopentyl and cyclohexyl.

Preferred examples of cycloalkyl-lower alkyl group whose ring portion may be substituted with lower alkyl as R<sup>60</sup> include cyclopropylmethyl, cyclobutylmethyl, 2-(1-methylcyclopropyl)ethyl, cyclopentylmethyl, (2,2-dimethylcyclopentyl)methyl, 1-cyclopentylethyl, cyclohexylmethyl and 1-cyclohexylethyl.

Preferred examples of cycloalkenyl-lower alkyl group as R<sup>60</sup> include cycloheptenyl and cyclononenyl.

Preferred examples of aralkyl group as R<sup>60</sup> include benzyl.

Preferred examples of R<sup>60</sup> include hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, cycloalkyl and cycloalkyl-lower alkyl whose ring portion may be substituted with lower alkyl.

R<sup>61</sup> and R<sup>71</sup> each independently stands for C<sub>1</sub>-C<sub>10</sub> alkyl, lower

alkenyl, cycloalkyl, cycloalkyl-lower alkyl whose ring portion may be substituted with lower alkyl, cycloalkenyl-lower alkyl or aralkyl; or R<sup>61</sup> and R<sup>71</sup> may together stand for optionally substituted trimethylene, tetramethylene, 2-butenylene, pentamethylene, 3-oxapentamethylene or 2,3-epoxytetramethylene group, the substituent being selected from the group consisting of oxo, hydroxyl, lower alkyl and lower alkoxy.

Preferred examples of C<sub>1</sub>-C<sub>10</sub> alkyl groups as R<sup>61</sup> and R<sup>71</sup> include C<sub>1</sub>-C<sub>6</sub> alkyl, in particular, methyl, ethyl, propyl and 2-methylbutyl.

Preferred examples of lower alkenyl as R<sup>61</sup> and R<sup>71</sup> include 2-propenyl and 3-butenyl.

Preferred example of cycloalkyl as R<sup>61</sup> and R<sup>71</sup> is cyclohexyl.

Preferred examples of cycloalkyl-lower alkyl whose ring portion may be substituted with lower alkyl as R<sup>61</sup> and R<sup>71</sup> include cyclopropylmethyl, cyclohexylmethyl, cycloheptylmethyl and cyclooctylmethyl, in particular, cyclopropylmethyl and cyclohexylmethyl, inter alia, cyclopropylmethyl.

Preferred examples of cycloalkenyl-lower alkyl as R<sup>61</sup> and R<sup>71</sup> include cycloheptenylmethyl and cyclononenylmethyl.

Preferred examples of aralkyl as R<sup>61</sup> and R<sup>71</sup> include benzyl.

“Trimethylene Optionally substituted trimethylene, tetramethylene, 2-butenylene, pentamethylene, 3-oxapentamethylene or 2,3-epoxytetramethylene group, the substituent being selected from the group consisting of oxo, hydroxyl, lower alkyl and lower alkoxy” means unsubstituted trimethylene, tetramethylene, [[2-butenylene] 2-butenylene, pentamethylene, 3-oxapentamethylene or 2,3-epoxytetramethylene; or those having one, two or more, preferably one or two substituents which may be same or different, which are selected from the group consisting of oxo, hydroxyl, lower alkyl and lower alkoxy, at optional substitutable position or positions.

Preferred examples of lower alkyl serviceable as the above substituent include methyl, ethyl and propyl, in particular, methyl.



Preferred examples of lower alkoxy serviceable as the above substituent include methoxy and ethoxy.

Preferred examples of the above substituents include lower alkyl groups.

5           Among the trimethylene, tetramethylene, 2-butenylene, pentamethylene, 3-oxapentamethylene or 2,3-epoxytetramethylene groups, for example, tetramethylene, 2-butenylene, pentamethylene or 2,3-epoxytetramethylene are preferred.

Hence, among the optionally substituted trimethylene,  
10 tetramethylene, 2-butenylene, pentamethylene, 3-oxapentamethylene or 2,3-epoxytetramethylene represented jointly by  $R^{61}$  and  $R^{71}$ , those preferred include unsubstituted tetramethylene, 2-butenylene, pentamethylene and 2,3-epoxytetramethylene; and lower alkyl-substituted tetramethylene, 2-butenylene, pentamethylene and  
15 2,3-epoxytetramethylene.

Preferred embodiments of  $R^{61}$  and  $R^{71}$  include: those wherein  $R^{61}$  and  $R^{71}$  each independently is selected from  $C_1$ - $C_{10}$  alkyl, lower alkenyl or cycloalkyl-lower alkyl; or  $R^{61}$  and  $R^{71}$  together stand for trimethylene, tetramethylene, 2-butenylene, pentamethylene,  
20 3-oxapentamethylene or 2,3-epoxytetramethylene which optionally have substituent(s) selected from the group consisting of oxo, hydroxyl, lower alkyl and lower alkoxy. More specifically, the preferred embodiments include those wherein both  $R^{61}$  and  $R^{71}$  are methyl, ethyl, propyl, 2-propenyl or cyclopropylmethyl;  $R^{61}$  is  
25 cyclohexylmethyl and  $R^{71}$  is methyl; or  $R^{61}$  and  $R^{71}$  together form tetramethylene, 2-butenylene, pentamethylene or 2,3-epoxytetramethylene group.

As  $Q^-$ , for example, anions formed from halogen atoms such as  $Cl^-$ ,  $Br^-$  and  $I^-$  are preferred;

30           s means 0, 1 or 2; and  $Q^-$  stands for anion, convenient s being 1.

$Ar^1$ ,  $Ar^2$  and  $Ar^3$  each independently stands for optionally substituted phenyl, the substituent being selected from the group

consisting of halogen, hydroxyl, lower alkyl, lower alkenyl, lower alkoxy, carbamoyl, lower alkylcarbamoyl and di-lower alkylcarbamoyl.

Said “optionally substituted phenyl, the substituent being  
5 selected from the group consisting of halogen, hydroxyl, lower alkyl, lower alkenyl, lower alkoxy, carbamoyl, lower alkylcarbamoyl and di-lower alkylcarbamoyl” mean unsubstituted phenyl or phenyl having substituent(s) at substitutable, optional position(s), said one, two or more, preferably one or two same or different substituents  
10 being selected from the group consisting of halogen, hydroxyl, lower alkyl, lower alkenyl, lower alkoxy, carbamoyl, lower alkylcarbamoyl and di-lower alkylcarbamoyl.

Among the halogen atoms as the substituent, for example, fluorine, chlorine and bromine, inter alia, fluorine, are preferred.

15 Among the lower alkyl groups as the substituent, for example, methyl, ethyl and propyl are preferred.

Among the lower alkenyl groups as the substituent, for example, vinyl, 1-propenyl and 2-propenyl are preferred.

20 Among the lower alkoxy groups as the substituent, for example, methoxy and ethoxy are preferred.

Among the lower alkylcarbamoyl groups as the substituent, for example, methylcarbamoyl and ethylcarbamoyl are preferred.

25 Among the di-lower alkylcarbamoyl groups as the substituent, for example, dimethylcarbamoyl and diethylcarbamoyl are preferred.

As the substituent, halogen atoms and lower alkyl groups are preferred.

30 As Ar<sup>1</sup>, Ar<sup>2</sup> and Ar<sup>3</sup>, independently of each other, phenyl which is optionally substituted with halogen or lower alkyl are preferred. In particular, such cases wherein all of them are unsubstituted phenyl, or phenyl substituted with halogen, inter alia, fluorine, are preferred.

The suffix k stands for 0 or 1; and m and n, each

independently, 0, 1 or 2, preferred n being 1 or 2.

R<sup>1</sup> stands for hydrogen or optionally substituted lower alkyl, the substituent being selected from the group consisting of hydroxyl, amino, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl and  
5 imidazolyl.

Said "optionally substituted lower alkyl, the substituent being selected from the group consisting of hydroxyl, amino, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl and imidazolyl" mean unsubstituted lower alkyl groups as above-named  
10 or the lower alkyl groups having substituent(s) at substitutable, optional position(s), said one, two or more, preferably one or two same or different substituents being selected from the group consisting of hydroxyl, amino, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl and imidazolyl.

15 Among the above lower alkylcarbamoyl as the substituent, for example, methylcarbamoyl and ethylcarbamoyl are preferred.

Among the di-lower alkylcarbamoyl as the substituent, for example, dimethylcarbamoyl and diethylcarbamoyl are preferred.

Preferred substituents include hydroxyl, amino and  
20 carbamoyl groups.

As the R<sup>1</sup> lower alkyl, for example, methyl, ethyl and propyl are preferred.

Thus, specific examples of R<sup>1</sup> include hydrogen, methyl, ethyl, propyl, hydroxymethyl, 2-hydroxyethyl, aminomethyl, 2-aminoethyl, carbamoylmethyl, 2-carbamoylethyl, methylcarbamoylmethyl, 2-methylcarbamoylethyl, dimethylcarbamoylmethyl, 2-dimethyl-  
25 carbamoylethyl, 4-imidazolylmethyl and 2-(4-imidazolyl)ethyl. Of those, hydrogen, methyl, ethyl, propyl, hydroxymethyl, 2-hydroxyethyl, aminomethyl, 2-aminoethyl, carbamoylmethyl and  
30 2-carbamoylethyl are preferred, in particular, hydrogen is preferred.

R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> each independently stands for hydrogen or optionally substituted lower alkyl, the substituent being selected from the group consisting of hydroxyl, amino, carbamoyl, lower

alkylcarbamoyl, di-lower alkylcarbamoyl and imidazolyl, or  $R^2$  and  $R^3$ , or  $R^4$  and  $R^5$ , may together stand for, independently of each other, optionally substituted trimethylene, propenylene, tetramethylene or 2-butenylene group, the substituent being selected from the group  
5 consisting of oxo, hydroxyl, amino, lower alkoxy, lower alkanoyloxy, lower alkylamino, di-lower alkylamino, (imino-lower alkyl)amino, lower alkanoylamino, lower alkoxycarbonylamino, (lower alkylcarbamoyl)amino, lower alkylsulfonylamino, guanidino, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower  
10 alkylcarbamoyl, imidazolyl and a group represented by  $-R^7$ .

Said "optionally substituted lower alkyl, the substituent being selected from the group consisting of hydroxyl, amino, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl and imidazolyl" mean unsubstituted lower alkyl groups as above-named  
15 or the lower alkyl groups having substituent(s) at substitutable, optional ~~positions(s)~~ position(s), said one, two or more, preferably one or two same or different substituents being selected from the group consisting of hydroxyl, amino, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl and imidazolyl.

20 Among the lower alkylcarbamoyl as the substituent, for example, methylcarbamoyl and ethylcarbamoyl are preferred.

Among the di-lower alkylcarbamoyl as the substituent, for example, dimethylcarbamoyl and diethylcarbamoyl are preferred.

Preferred substituents include hydroxyl, amino, carbamoyl  
25 and imidazolyl groups.

As the lower alkyl groups as  $R^2$ ,  $R^3$ ,  $R^4$  or  $R^5$ , for example, methyl, ethyl and propyl are preferred.

Thus, examples of the optionally substituted lower alkyl as  $R^2$ ,  $R^3$ ,  $R^4$  or  $R^5$  are same to those earlier named optionally substituted  
30 lower alkyl groups as  $R^1$ , among which methyl, ethyl, propyl, hydroxymethyl, 2-hydroxyethyl, aminomethyl, 2-aminoethyl, carbamoylmethyl, 2-carbamoylethyl and 4-imidazolylmethyl, inter alia, methyl and 4-imidazolylmethyl, are preferred.

Said "optionally substituted trimethylene, propenylene, tetramethylene or 2-butenylene group, the substituent being selected from the group consisting of oxo, hydroxyl, amino, lower alkoxy, lower alkanoyloxy, lower alkylamino, di-lower alkylamino, (imino-lower alkyl)amino, lower alkanoylamino, lower alkoxycarbonylamino, (lower alkylcarbamoyl)amino, lower alkylsulfonylamino, guanidino, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, imidazolyl and a group represented by -R<sup>7</sup>" mean unsubstituted trimethylene, propenylene, tetramethylene and 2-butenylene groups, or those having substituent(s) at substitutable, optional position(s), said one, two or more, preferably one or two same or different substituents being selected from the group consisting of oxo, hydroxyl, amino, lower alkoxy, lower alkanoyloxy, lower alkylamino, di-lower alkylamino, (imino-lower alkyl)amino, lower alkanoylamino, lower alkoxycarbonylamino, (lower alkylcarbamoyl)-amino, lower alkylsulfonylamino, guanidino, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, imidazolyl and a group represented by -R<sup>7</sup>.

Among the lower alkoxy as the substituent, for example, methoxy, ethoxy, propoxy and tert-butoxy are preferred.

Among the lower alkanoyloxy as the substituent, for example, acetoxy and propionyloxy are preferred.

Among the lower alkylamino as the substituent, for example, methylamino, ethylamino and propylamino are preferred.

Among the di-lower alkylamino as the substituent, for example, dimethylamino and diethylamino are preferred.

Among the (imino-lower alkyl)amino as the substituent, for example, formimidoylamino, acetimidoylamino and propanimidoylamino are preferred.

Among the lower alkanoylamino as the substituent, for example, acetylamino and propionylamino are preferred.

Among the lower alkoxycarbonylamino as the substituent, for example, methoxycarbonylamino, ethoxycarbonylamino and

propoxycarbonylamino are preferred.

Among the (lower alkylcarbamoyl)amino as the substituent, for example, (methylcarbamoyl)amino, (ethylcarbamoyl)amino and (propylcarbamoyl)amino are preferred.

5        Among the lower alkylsulfonylamino as the substituent, for example, methylsulfonylamino, ethylsulfonylamino and propylsulfonylamino are preferred.

      Among the lower alkoxycarbonyl as the substituent, for example, methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl are  
10 preferred.

      Among the lower alkylcarbamoyl as the substituent, for example, methylcarbamoyl, ethylcarbamoyl and propylcarbamoyl are preferred.

      Among di-lower alkylcarbamoyl as the substituent, for  
15 example, dimethylcarbamoyl and diethylcarbamoyl are preferred.

      R<sup>7</sup> stands for optionally substituted lower alkyl group, the substituent being selected from the group consisting of hydroxyl, amino, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, lower alkoxycarbonyl and imidazolyl.

20        “Optionally substituted lower alkyl group, the substituent being selected from the group consisting of hydroxyl, amino, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, lower alkoxycarbonyl and imidazolyl” means unsubstituted lower alkyl groups as above-named or the lower alkyl groups having  
25 substituent(s) at substitutable, optional position(s), said one, two or more, preferably one or two same or different substituents being selected from the group consisting of hydroxyl, amino, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, lower alkoxycarbonyl and imidazolyl.

30        Among the lower alkylcarbamoyl as the substituent, for example, methylcarbamoyl, ethylcarbamoyl and propylcarbamoyl are preferred.

      Among the di-lower alkylcarbamoyl as the substituent, for

example, dimethylcarbamoyl and diethylcarbamoyl are preferred.

Among the lower alkoxycarbonyl as the substituent, for example, methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl are preferred.

5           As the substituent groups, for example, hydroxyl, amino and carbamoyl are preferred.

          As the lower alkyl groups as  $R^7$ , for example, methyl and ethyl are preferred.

          Hence, preferred examples of  $R^7$  include methyl, ethyl, propyl,  
10   hydroxymethyl, 2-hydroxyethyl, aminomethyl, 2-aminoethyl, carbamoylmethyl, 2-carbamoylethyl, methylcarbamoylmethyl, 2-methylcarbamoylethyl, dimethylcarbamoylmethyl, 2-dimethylcarbamoylethyl, methoxycarbonylmethyl, 2-methoxycarbonylethyl, 4-imidazolylmethyl and 2-(4-imidazolyl)ethyl. In particular, methyl,  
15   ethyl, hydroxymethyl, aminomethyl and carbamoylmethyl are preferred.

          As the substituent(s) on trimethylene, propenylene, tetramethylene or 2-butenylene, oxo, hydroxyl, amino, lower alkoxy, lower alkylamino and di-lower alkylamino, inter alia, hydroxyl and  
20   amino, are preferred.

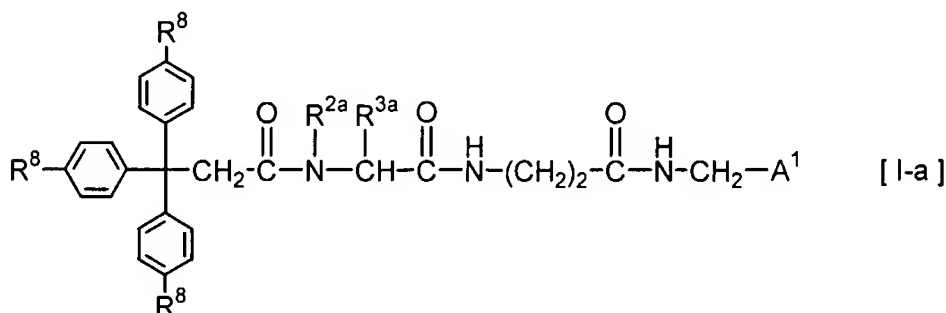
          Among trimethylene, propenylene, tetramethylene and 2-butenylene groups, trimethylene is the preferred.

          Accordingly, among those optionally substituted trimethylene, propenylene, tetramethylene and 2-butenylene formed  
25   together by  $R^2$  and  $R^3$ , or  $R^4$  and  $R^5$ , unsubstituted trimethylene and hydroxyl- or amino-substituted trimethylene are particularly preferred.

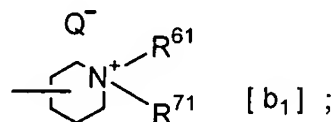
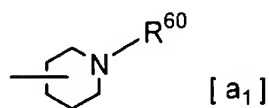
          Preferred embodiments of  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  include one wherein  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are hydrogen atoms at the same time; those  
30   wherein either one of  $R^2$  and  $R^3$  is hydrogen and the other is an optionally substituted lower alkyl, the substituent being selected from the group consisting of hydroxyl, amino, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl and imidazolyl, and both  $R^4$

and R<sup>5</sup> are hydrogen atoms; and those wherein R<sup>2</sup> and R<sup>3</sup>, or R<sup>4</sup> and R<sup>5</sup> together stand for, independently of each other, optionally substituted trimethylene, the substituent being selected from the group consisting of oxo, hydroxyl, amino, lower alkoxy, lower alkanoyloxy, lower  
 5 alkylamino, di-lower alkylamino, (imino-lower alkyl)amino, lower alkanoylamino, lower alkoxycarbonylamino, (lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, imidazolyl and -R<sup>7</sup> (here R<sup>7</sup> has the earlier defined signification).

Among the compounds represented by the general formula [I],  
 10 therefore, for example those in which Ar<sup>1</sup>, Ar<sup>2</sup> and Ar<sup>3</sup> are each independently phenyl which may be halogen- or lower alkyl-substituted, n is 1 or 2, s is 1, and R<sup>1</sup> is hydrogen, are preferred. In particular, the compounds represented by the following general formula [I-a]:



[wherein A<sup>1</sup> stands for a group represented by the formula [a<sub>1</sub>]  
 or [b<sub>1</sub>]



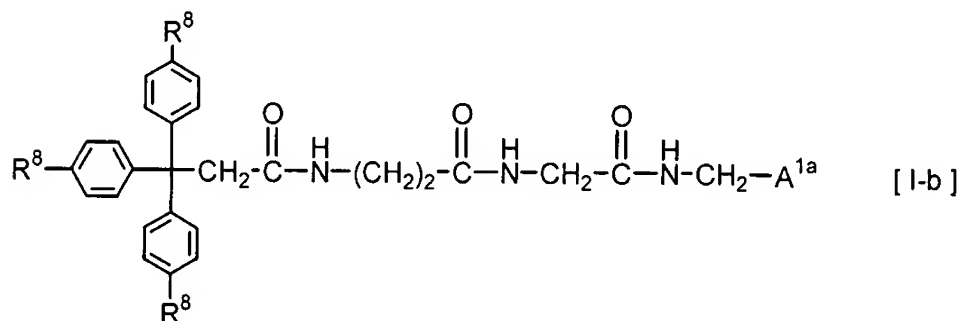
25 R<sup>2a</sup> and R<sup>3a</sup> each independently stands for hydrogen, or optionally substituted lower alkyl, the substituent being selected from hydroxyl, amino, carbamoyl, lower



alkylcarbamoyl, di-lower alkylcarbamoyl and imidazolyl;  $R^8$  stands for hydrogen, halogen or lower alkyl;  $R^{60}$ ,  $R^{61}$ ,  $R^{71}$  and  $Q^-$  have the earlier defined significations];

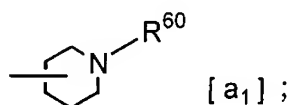
the compounds represented by the general formula [I-b]:

5



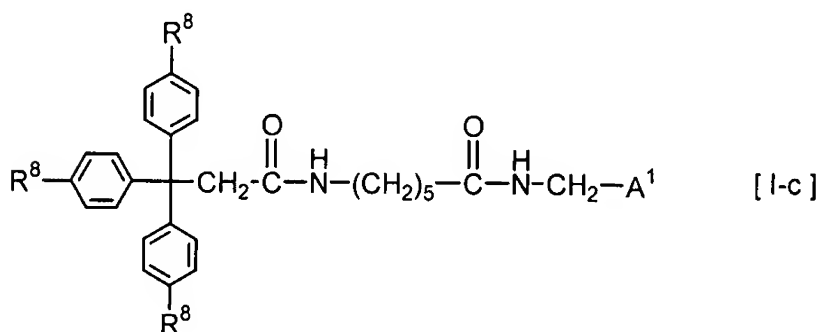
[wherein  $A^{1a}$  stands for a group of the formula  $[a_1]$

10



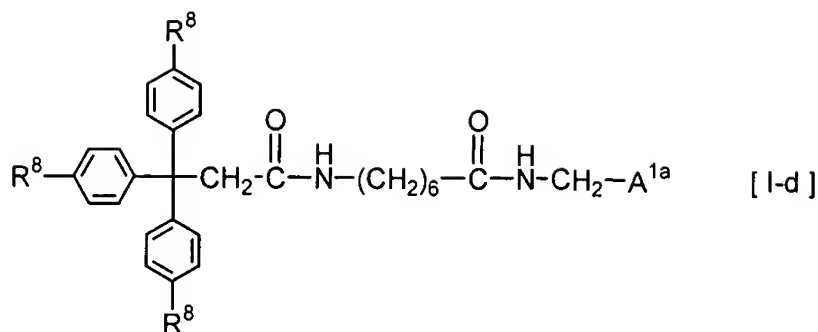
and  $R^8$  and  $R^{60}$  have the earlier defined significations];  
the compounds represented by the general formula [I-c]:

15



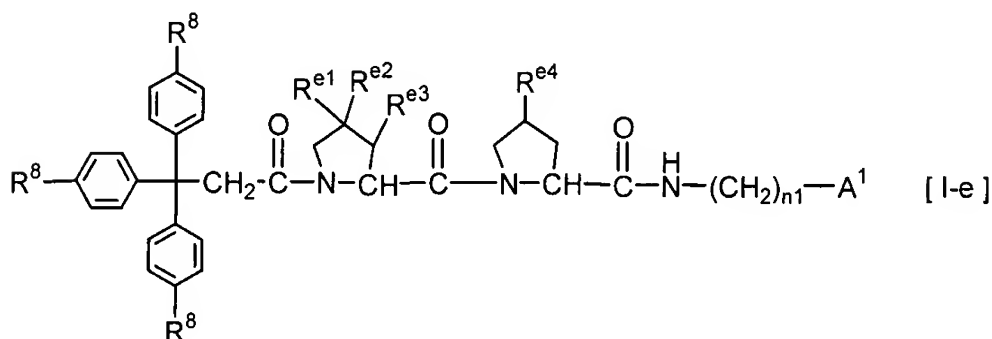
[in which  $A^1$  and  $R^8$  have the earlier defined significations];  
the compounds represented by the general formula [I-d]:

20



[in which A<sup>1a</sup> and R<sup>8</sup> have the earlier defined significations];  
and the compounds represented by the general formula [I-e]

5



[in which n1 stands for 1 or 2; R<sup>e1</sup>, R<sup>e2</sup>, R<sup>e3</sup> and R<sup>e4</sup> each  
independently stands for hydrogen, hydroxyl, amino, lower  
alkoxy, lower alkanoyloxy, lower alkylamino, di-lower  
alkylamino, (imino-lower alkyl)amino, lower alkanoylamino,  
lower alkoxycarbonylamino, (lower alkylcarbamoyl)amino,  
lower alkylsulfonylamino, guanidino, lower alkoxycarbonyl,  
carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl,  
imidazolyl and a group represented by -R<sup>7</sup>; or R<sup>e1</sup> and R<sup>e2</sup>  
together signify oxo group; and A<sup>1</sup>, R<sup>7</sup> and R<sup>8</sup> have the earlier  
defined significations]

are preferred.

Among the compounds represented by the general formula  
[I-a], the preferred are those in which R<sup>2a</sup> is hydrogen and R<sup>3a</sup> is  
hydrogen, methyl, ethyl, propyl, hydroxymethyl, 2-hydroxyethyl,

aminomethyl, 2-aminoethyl, carbamoylmethyl, 2-carbamoylethyl or 4-imidazolylmethyl, in particular, hydrogen or 4-imidazolylmethyl; or those in which  $R^{2a}$  is methyl and  $R^{3a}$  is hydrogen.

Among the compounds represented by the general formula [I-e], the preferred are those in which  $R^{e1}$ ,  $R^{e2}$ ,  $R^{e3}$  and  $R^{e4}$  each independently is hydrogen, hydroxyl, amino, methoxy, ethoxy, propoxy, tert-butoxy, acetoxy, methylamino, ethylamino, propylamino, dimethylamino and diethylamino, or those in which  $R^{e1}$  and  $R^{e2}$  together form oxo group and  $R^{e3}$  and  $R^{e4}$  both are hydrogen atoms. In particular, the compounds in which  $R^{e1}$  is hydroxyl or amino, preferably hydroxyl, and  $R^{e2}$ ,  $R^{e3}$  and  $R^{e4}$  are hydrogen atoms at the same time; those in which both  $R^{e1}$  and  $R^{e3}$  are hydroxyl groups and both  $R^{e2}$  and  $R^{e4}$  are hydrogen atoms; or those in which both  $R^{e1}$  and  $R^{e2}$  are hydroxyl groups and both  $R^{e3}$  and  $R^{e4}$  are hydrogen atoms are advantageous. Inter alia, the compounds where  $A^1$  is a group represented by the formula [b<sub>1</sub>],  $R^{61}$  and  $R^{71}$  are at the same time methyl, ethyl, propyl, 2-propenyl or cyclopropylmethyl, in particular, ethyl, propyl or cyclopropylmethyl; or  $R^{61}$  is cyclohexylmethyl and  $R^{71}$  is methyl; or  $R^{61}$  and  $R^{71}$  together form tetramethylene, 2-butenylene or pentamethylene, in particular, tetramethylene or 2-butenylene, can be advantageously used.

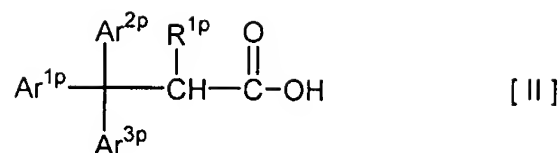
Referring to those general formulae [I-a], [I-b], [I-c], [I-d] and [I-e], convenient  $R^8$  is, for example, hydrogen or halogen, in particular, hydrogen or fluorine.

Now processes for preparing the compounds of the present invention are explained.

The compounds of the present invention can be prepared by the following processes or those as shown in working examples, it being understood that the preparation processes of compounds of this invention are not limited to those reaction examples.

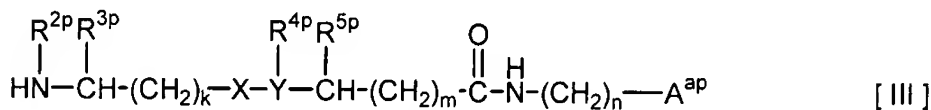
#### Production process 1

Carboxylic acid of the general formula [II]:

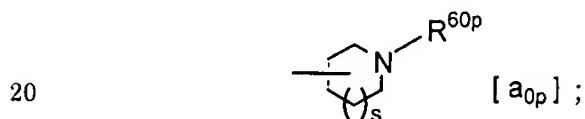


5 [in which Ar<sup>1p</sup>, Ar<sup>2p</sup> and Ar<sup>3p</sup> each independently stands for  
 optionally substituted phenyl, the substituent being selected  
 from the group consisting of halogen, lower alkyl, lower  
 alkenyl, lower alkoxy and di-lower alkylcarbamoyl and  
 optionally protected hydroxyl, carbamoyl and lower  
 10 alkylcarbamoyl; and R<sup>1p</sup> stands for hydrogen or optionally  
 substituted lower alkyl, the substituent being selected from  
 the group consisting of di-lower alkylcarbamoyl, optionally  
 protected hydroxyl, amino, carbamoyl, lower alkylcarbamoyl  
 and imidazolyl groups]

or salt or reactive derivative thereof is reacted with a compound of the  
 general formula [III]:



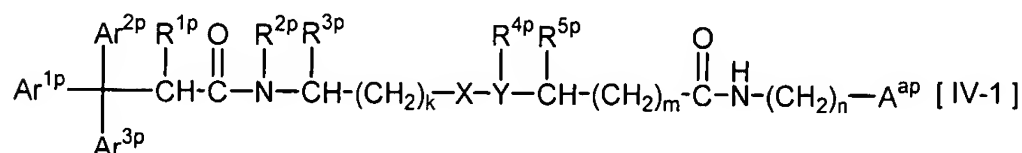
[in which A<sup>ap</sup> stands for a group of the formula [a<sub>op</sub>]



20 R<sup>2p</sup>, R<sup>3p</sup>, R<sup>4p</sup> and R<sup>5p</sup> each independently stands for hydrogen or  
 optionally substituted lower alkyl, the substituent being  
 selected from the group consisting of di-lower alkylcarbamoyl  
 and optionally protected hydroxyl, amino, carbamoyl, lower  
 25 alkylcarbamoyl and imidazolyl groups, or R<sup>2p</sup> and R<sup>3p</sup>, or R<sup>4p</sup>  
 and R<sup>5p</sup>, together form, each independently of the other pair,  
 optionally substituted trimethylene, propenylene,

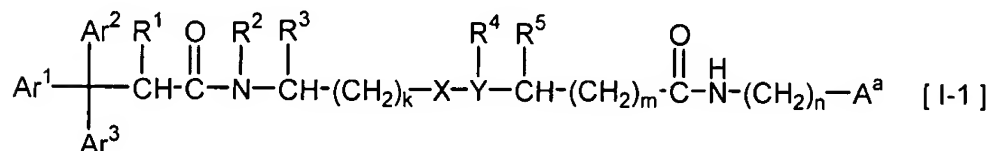
tetramethylene or 2-butenylene, the substituent being selected from the group consisting of lower alkoxy, lower alkanoyloxy, di-lower alkylamino, lower alkoxy carbonyl, di-lower alkylcarbamoyl, a group represented by  $-R^{7p}$  and optionally protected oxo, hydroxyl, amino, lower alkylamino, (imino-lower alkyl)amino, lower alkanoylamino, lower alkoxy carbonylamino, (lower alkylcarbamoyl)amino, lower alkylsulfonylamino, guanidino, carbamoyl, lower alkylcarbamoyl and imidazolyl groups;  $R^{7p}$  stands for optionally substituted lower alkyl, the substituent being selected from the group consisting of optionally protected hydroxyl, amino, carbamoyl, lower alkylcarbamoyl and imidazolyl groups;  $R^{60p}$  stands for imino-protecting group,  $C_1-C_{10}$  alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl whose ring portion being optionally substituted with lower alkyl, cycloalkenyl-lower alkyl or aralkyl; and k, m, n, s, X and Y have the earlier defined significations]

or salt thereof, to form a compound represented by the general formula [IV-1]

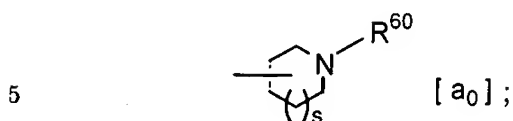


[in which  $A^{ap}$ ,  $Ar^{1p}$ ,  $Ar^{2p}$ ,  $Ar^{3p}$ , k, m, n,  $R^{1p}$ ,  $R^{2p}$ ,  $R^{3p}$ ,  $R^{4p}$ ,  $R^{5p}$ , X and Y have the earlier defined significations]

or a salt thereof, and if necessary the protective group(s) are removed to produce a compound represented by the general formula [I-1]



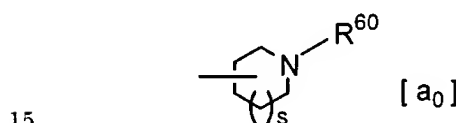
[in which A<sup>a</sup> stands for a group of the formula [a<sub>0</sub>]



Ar<sup>1</sup>, Ar<sup>2</sup>, Ar<sup>3</sup>, k, m, n, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>60</sup>, s, X and Y have the earlier defined significations]

or salts thereof.

10 The above production process 1 is the process for producing, among the compounds of the present invention which are represented by the general formula [I], those in which A in said general formula is a group represented by the formula [a<sub>0</sub>]



[in which R<sup>60</sup> and s have the earlier defined significations], i.e., the compounds expressed by the earlier given general formula [I-1].

Where the reactants in the above reaction contain oxo, hydroxyl, amino or imino groups which do not participate in the reaction, those groups are preferably suitably protected by respective protective groups before the reaction, and are deprotected [[afterthe]] after the reaction.

Examples of "oxo-protective group" include acetals and ketals such as ethylene ketal, trimethylene ketal and dimethyl ketal.

25 Examples of "hydroxyl-protective group" include alkyl such as tert-butyl; substituted silyls such as trimethylsilyl, tert-butyl dimethylsilyl and tert-butyl diphenylsilyl; lower alkoxy methyl such as methoxymethyl and 2-methoxyethoxymethyl; tetrahydropyranyl; trimethylsilylethoxymethyl; aralkyl such as benzyl, 30 p-methoxybenzyl, [[2,3-dimethoxybenzyl]] 2,3-dimethoxybenzyl, [[o-nitrogenyl]] o-nitrobenzyl, p-nitrobenzyl and triphenylmethyl;

and acyl such as formyl and acetyl. In particular, tert-butyl, benzyl, methoxymethyl, tetrahydropyranyl, triphenylmethyl, trimethylsilylethoxymethyl, tert-butyldimethylsilyl and acetyl groups are preferred.

5           Examples of “amino- or imino-protective group” include aralkyl such as benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and triphenylmethyl; lower alkanoyl such as formyl, acetyl, propionyl, butyryl and pivaloyl; benzoyl; arylalkanoyl such as phenylacetyl and phenoxyacetyl; lower  
10   alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl and tert-butoxycarbonyl; aralkyloxycarbonyl such as benzyloxycarbonyl, p-nitrobenzyloxycarbonyl and phenethyloxycarbonyl; lower alkylsilyl such as trimethylsilyl and tert-butyldimethylsilyl; phthaloyl; and aralkylidene such as benzylidene,  
15   p-chlorobenzylidene and o-nitrobenzylidene. In particular, acetyl, pivaloyl, benzoyl, ethoxycarbonyl, benzyloxycarbonyl and tert-butoxycarbonyl groups are preferred.

          The reaction of a carboxylic acid of the general formula [II] or salt or reactive derivative thereof with a compound expressed by the  
20   general formula [III] or salt thereof is usually carried out using 1-5 mols, preferably 1-2 mols, of the carboxylic acid of the formula [II] or salt or reactive derivative thereof, per mol of the compound of the formula [III] or salt thereof.

“Salt” of said carboxylic acid of the formula [II] means base addition salt at the carboxyl group, examples of which include alkali metal salt such as sodium salt and potassium salt; alkaline earth metal salt such as calcium salt and magnesium salt; ammonium salt; and organic amine salt such as trimethylamine salt, triethylamine salt, dicyclohexylamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, procaine salt and  
[[N,N-dibenzylethylenediamine]] N,N'-dibenzylethylenediamine

salt.

Examples of "reactive derivative" of the carboxylic acid of the formula [II] are mixed acid anhydrides, active esters and active amides.

5           Where said carboxylic acid of the formula [II] or salt thereof is used in the reaction, the reaction is preferably carried out in the presence of a condensing agent such as, for example, N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, diphenylphosphoryl azide and dipyridyldisulfide-triphenylphosphin, 10 in particular, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

The use rate of the condensing agent is not strictly limited, while it is usually in the range of 1-5 mols, preferably 1-2 mols, per mol of the carboxylic acid of the formula [II] or salt thereof.

15           The reaction is usually carried out in an inert solvent, examples of which include diethyl ether, tetrahydrofuran, N,N-dimethylformamide, dioxane, benzene, toluene, chlorobenzene, methylene chloride, chloroform, carbon tetrachloride, dichloroethane and trichloroethylene; and mixtures of those solvents. In particular, 20 diethyl ether, tetrahydrofuran, N,N-dimethylformamide, chloroform and dioxane are preferred.

The reaction temperature usually ranges from  $-70^{\circ}\text{C}$  to the boiling point of the solvent used in the reaction, preferably  $-20^{\circ}\text{C}$  –  $100^{\circ}\text{C}$ .

25           The reaction time usually ranges from 5 minutes to 7 days, preferably from 10 minutes to 24 hours.

The reaction may also be carried out in the presence of a base, for smooth progress of the reaction.

30           Examples of useful base include aliphatic tertiary amine such as triethylamine and diisopropylethylamine; and aromatic amines such as pyridine, 4-dimethylaminopyridine and quinoline. Of those, triethylamine and 4-dimethylaminopyridine are preferred.

The use rate of said ~~base~~base can be within a range of 1-5



mols, preferably 1-2 mols, per mol of the carboxylic acid expressed by the formula [II] or salt or reactive derivative thereof.

Mixed acid anhydride of carboxylic acid of the formula [II] can be obtained by reacting carboxylic acid of the formula [II] with, for  
5 example, alkyl chlorocarbonate such as ethyl chlorocarbonate;  
aliphatic carboxylic acid chloride such as acetyl chloride, pivaloyl  
chloride and the like, according to usual method.

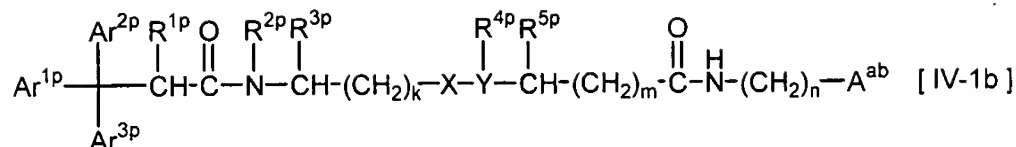
Active esters of carboxylic acid of the formula [II] can be  
obtained by reacting the carboxylic acid of said formula [II] with, for  
10 example, an N-hydroxy compound such as N-hydroxysuccinimide,  
N-hydroxyphthalimide or 1-hydroxybenzotriazole; or a phenol  
compound such as 4-nitrophenol, 2,4-dinitrophenol, 2,4,5-trichloro-  
phenol, pentachlorophenol or the like; in the presence of a condensing  
agent, e.g., N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethyl-  
15 aminopropyl)carbodiimide hydrochloride, diphenylphosphoryl azide  
or dipyridyl disulfide-triphenylphosphine, according to usual method.

Active amide of the carboxylic acid of the formula [II] can be  
obtained by reacting the carboxylic acid of formula [II] with  
1,1'-carbonyldiimidazole, 1,1'-carbonylbis(2-methylimidazole) or the  
20 like according to usual methods.

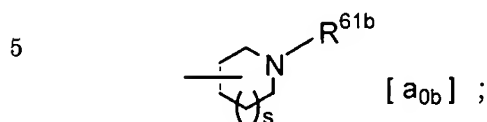
After completion of the reaction, ordinary treatment is given  
to provide crude product of a compound expressed by the general  
formula [IV-1], which is optionally purified according to usual method  
and further if necessary subjected to a reaction for removing  
25 protective group(s) of oxo, hydroxyl, amino or imino, to provide a  
compound of the formula [I-1].

Method for removing the protective group(s) differs depending  
on the kind of the protective group and stability of the object  
compound [I-1], but those methods known per se may be employed, for  
30 example, those taught in Protective Groups in Organic Synthesis, T.W.  
Greene, John Wiley & Sons Co. (1981) or methods analogous thereto,  
for example, solvolysis using an acid or base, that is, using for  
example 0.01 mol – a large excess of an acid, preferably trifluoroacetic





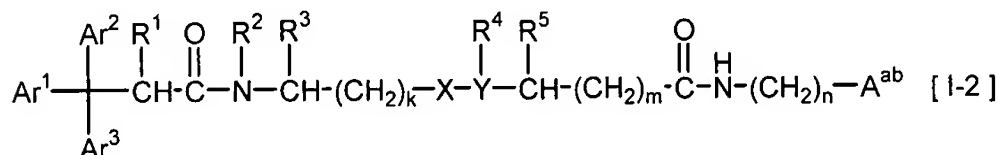
[in which A<sup>ab</sup> signifies a group represented by the formula [a<sub>0b</sub>]



R<sup>61b</sup> signifies C<sub>1</sub>-C<sub>10</sub> alkyl, lower alkenyl, cycloalkyl, cycloalkyl-  
lower alkyl whose ring portion may be substituted with lower  
10 alkyl, cycloalkenyl-lower alkyl or aralkyl; Ar<sup>1p</sup>, Ar<sup>2p</sup>, Ar<sup>3p</sup>, k, m, n,  
R<sup>1p</sup>, R<sup>2p</sup>, R<sup>3p</sup>, R<sup>4p</sup>, R<sup>5p</sup>, s, X, and Y have the earlier defined  
significations]

or a salt thereof, and if necessary removing the protective groups, a  
compound of the general formula [I-2]:

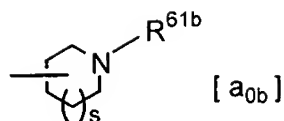
15



20 [in which A<sup>ab</sup>, Ar<sup>1</sup>, Ar<sup>2</sup>, Ar<sup>3</sup>, k, m, n, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, s, X and  
Y have the earlier defined significations]

or a salt thereof can be produced.

The production process 2 is a process for producing, among  
the compounds of the present invention represented by the general  
formula [I], those in which A is the group expressed by the formula  
25 [a<sub>0b</sub>]:



[in which  $R^{61b}$  and  $s$  have the earlier defined significations],  
i.e., the compounds expressed by the general formula [I-2].

5 Said "C<sub>1</sub>-C<sub>10</sub> alkylidene, lower alkenylidene, cycloalkylidene, cycloalkyl-lower alkylidene whose ring portion may be substituted with lower alkyl, cycloalkenyl-lower alkylidene or aralkylidene" as  $R^{61a}$  mean those which are capable of becoming the corresponding "C<sub>1</sub>-C<sub>10</sub> alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl whose  
10 ring portion may be substituted with lower alkyl, cycloalkenyl-lower alkyl or aralkyl", respectively, after completion of the above reaction.

The reaction of a compound represented by the general formula [IV-1a] or a salt thereof with a compound represented by the general formula [V] under reducing conditions is a so-called reductive  
15 ~~alkylation~~ alkylation reaction of an amino group, and conducted using a mol or molar excess, preferably 1-2 mols, of the compound of the general formula [V] per mol of the compound of the general formula [IV-1a] or salt thereof, in the presence of a reducing agent or under catalytic reduction, in an inert solvent which has no adverse effect on  
20 the reaction.

As the inert solvent, for example, alcohols such a methanol or ethanol; ethers such as diethyl ether, methyl tert-butyl ether, tetrahydrofuran or dioxane; aromatic hydrocarbons such as benzene or toluene; halogenated hydrocarbons such as dichloroethane; or their  
25 mixtures can be named, in particular, methanol, ethanol, tetrahydrofuran, dichloroethane or toluene being preferred.

Where the reaction is carried out in the presence of a reducing agent, examples of useful reducing agent include complex metal hydrides such as sodium boron hydride, sodium cyanoboron  
30 hydride, aluminium lithium hydride, aluminium diisobutyl hydride and sodium triacetoxyboron hydride; in particular, sodium boron

hydride, sodium cyanoboron hydride or sodium triacetoxymethylboron hydride being preferred.

The use rate of said reducing agent is usually a mol to molar excess, preferably 1-10 mols, per mol of the compound represented by  
5 the general formula [IV-1a] or salt thereof.

The reaction temperature usually ranges from about -30°C to about 200°C, preferably from about 0°C to 100°C; and the reaction time usually ranges from an instant to 7 days, preferably from an instant to 24 hours.

10 Where the reaction is carried out under catalytic reduction, for example, palladium-carbon catalyst, Raney nickel catalyst or the like is used as the catalyst.

The hydrogen pressure in the catalytic reduction reaction is usually and conveniently from atmospheric to 2 atmospheres, and the  
15 use rate of the catalyst is usually from 1/100 to 1, preferably 1/100 - 1/10 by weight to the starting compound [IV-1a].

The reaction temperature usually ranges from about -30°C to 50°C, preferably from about 0°C to room temperature, and the reaction time usually ranges from an instant to 7 days, preferably  
20 from an instant to 24 hours.

As the means of reduction in this reaction, the above-described reduction method using the complex metal hydride is convenient.

This reaction may be conducted under weakly acidic  
25 conditions, in which Schiff base is easily formed. As examples of acid useful for pH control for that purpose include p-toluenesulfonic acid, hydrochloric acid, sulfuric acid, acetic acid and trifluoroacetic acid.

In this step it is also possible not to conduct the reaction in the presence of a reducing agent or under catalytic reduction, but to  
30 first react a compound of the general formula [IV-1a] or salt thereof with a compound of the general formula [V] to form an imine in advance, and then to subject said imine to a reducing reaction.

In the above reaction where such groups as oxo, hydroxyl,

amino or imino which do not participate in the reaction are present in the reactants, it is desirable to suitably protect them with protective groups of oxo, hydroxyl, amino or imino, respectively, before the reaction and to remove the protective groups ~~after the~~ after the reaction.

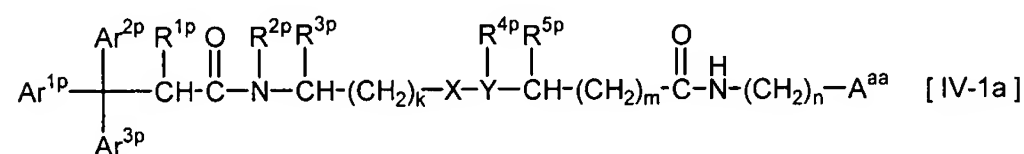
As the protective groups suitable for oxo, hydroxyl, amino or imino, those respective protective groups as described in relation to the production process 1 are applicable as they are.

Upon completion of the reaction, after removing the protective groups in the compound of the general formula [IV-1b] where they are present; or where no protective group is present in the product, without such an intervening treatment, the product is processed in the usual manner to produce a compound of the general formula [I-2].

For removing the protective groups and conducting the post-treatment, those methods as described as to the production process 1 are applicable.

### Production process 3

By following the steps of reacting a compound of the general formula [IV-1a]:

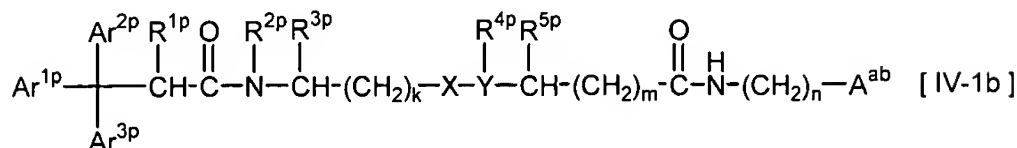


[in which A<sup>aa</sup>, Ar<sup>1p</sup>, Ar<sup>2p</sup>, Ar<sup>3p</sup>, k, m, n, R<sup>1p</sup>, R<sup>2p</sup>, R<sup>3p</sup>, R<sup>4p</sup>, R<sup>5p</sup>, X and Y have the earlier defined significations] or a salt thereof with a compound of the general formula [VI-1]



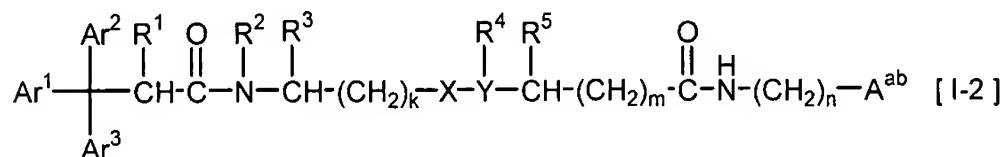
[in which L<sup>1</sup> signifies a leaving group, and R<sup>61b</sup> has the earlier defined signification]

to form a compound expressed by the general formula [IV-1b]



5                    [in which A<sup>ab</sup>, Ar<sup>1p</sup>, Ar<sup>2p</sup>, Ar<sup>3p</sup>, k, m, n, R<sup>1p</sup>, R<sup>2p</sup>, R<sup>3p</sup>, R<sup>4p</sup>, R<sup>5p</sup>,  
X and Y have the earlier defined significations]

or salt thereof, and if necessary removing the protective groups, a  
compound of the general formula [I-2]



10

[in which A<sup>ab</sup>, Ar<sup>1</sup>, Ar<sup>1</sup>, Ar<sup>2</sup>, Ar<sup>3</sup>, k, m, n, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, s, X  
and Y have the earlier defined significations]

or salt thereof can be produced .

15                    The production process 3 is a method for producing the  
compounds expressed by the general formula [I-2], same as above  
production process 2.

Examples of "leaving group" expressed by L<sup>1</sup> include halogen  
atoms such as chlorine, bromine and iodine; alkylsulfonyloxy groups  
20 such as methylsulfonyloxy; or arylsulfonyloxy groups such as  
p-toluenesulfonyloxy.

The reaction of a compound of the general formula [IV-1a] or  
a salt thereof with a compound of the general formula [IV-1] is usually  
conducted using a mol or molar excess, preferably 1-2 mols, of the  
25 compound of the formula [VI-1] per mol of the compound of formula  
[IV-1a] or salt thereof, in an inert solvent which is not detrimental to  
the reaction.

As such inert solvent, for example, ethers such as diethyl

ether, tetrahydrofuran and dioxane; aromatic hydrocarbons such as benzene, toluene, chlorobenzene and xylene; and aprotic polar solvents such as dimethylsulfoxide, N,N-dimethylformamide, acetonitrile and hexamethylphosphoric triamide; or mixtures of the  
5 foregoing can be used.

For smooth progress, the reaction may be carried out in the presence of base and/or a reaction assistant.

As the base, for example, alkali metal bicarbonates such as sodium hydrogencarbonate and potassium hydrogencarbonate; alkali  
10 metal carbonates such as sodium carbonate and potassium carbonate; tertiary aliphatic amines such as trimethylamine, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN);  
15 and aromatic amines such as pyridine, 4-dimethylaminopyridine, picoline, lutidine, quinoline and isoquinoline can be used. Of those, potassium carbonate, N,N-diisopropylethylamine and triethylamine are preferred.

The use rate of the base is usually a mol or molar excess,  
20 preferably 1-3 mols, per mol of the compound of the formula [IV-1a].

As assistant useful for the reaction, for example, alkali metal iodides such as lithium iodide, sodium iodide and potassium iodide may be named. Of these, potassium iodide is preferred.

The use rate of the assistant is usually from catalytic to  
25 excessive amount, preferably from catalytic amount to one equivalent, to the compound of the formula [IV-1a].

The reaction temperature may usually range from about 0°C to the boiling point of the solvent used in the reaction, and the reaction time may usually range from 10 minutes to 48 hours.

30 In the above reaction where such groups as oxo, hydroxyl, amino or imino which do not participate in the reaction are present in the reactants, it is desirable to suitably protect them with protective groups of oxo, hydroxyl, amino or imino, respectively, before the



reaction and to remove the protective groups ~~after~~ after the reaction.

As the protective groups suitable for oxo, hydroxyl, amino or imino, those respective protective groups as described in relation to  
 5 the production process 1 are applicable as they are.

Upon completion of the reaction, after removing the protective groups in the compound of the general formula [IV-1b] where they are present; or where no protective group is present in the product, without such an intervening treatment, the product is  
 10 processed in the usual manner to produce a compound of the general formula [I-2].

For removing the protective groups and conducting the post-treatment, those methods as described as to the production process 1 are applicable

15 Production process 4

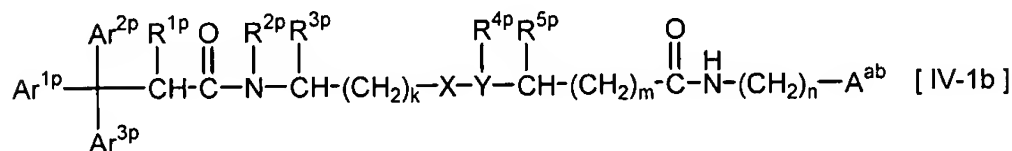
By following the steps of reacting a compound of the general formula [VI-2]:



20

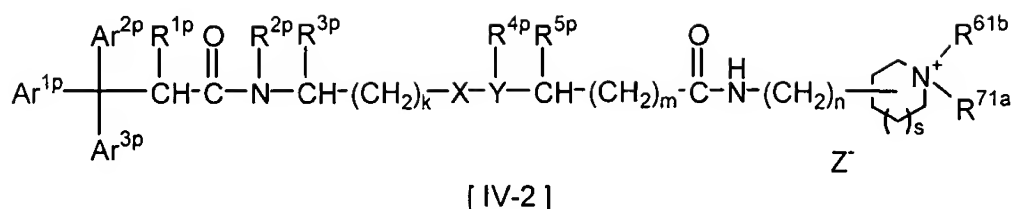
[in which  $L^2$  signifies a leaving group;  $R^{71a}$  signifies  $C_1-C_{10}$  alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl whose ring portion may be substituted with lower alkyl, cycloalkenyl-lower alkyl or aralkyl]

25 or a salt thereof with a compound of the general formula [IV-1b]:



[in which  $A^{ab}$ ,  $\text{Ar}^{1p}$ ,  $\text{Ar}^{2p}$ ,  $\text{Ar}^{3p}$ ,  $k$ ,  $m$ ,  $n$ ,  $R^{1p}$ ,  $R^{2p}$ ,  $R^{3p}$ ,  $R^{4p}$ ,  $R^{5p}$ ,  $s$ ,  
 30  $X$  and  $Y$  have the earlier defined significations]  
 or a salt thereof, to form a compound expressed by the general

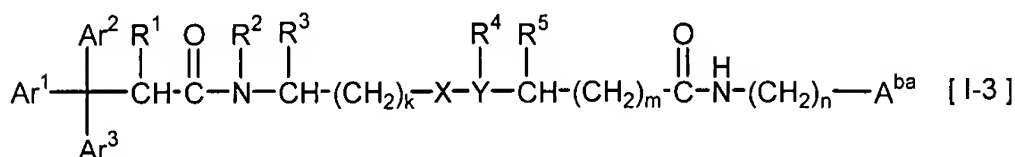
formula [IV-2]:



5 [in which Z<sup>-</sup> signifies anion; Ar<sup>1p</sup>, Ar<sup>2p</sup>, Ar<sup>3p</sup>, k, m, n, R<sup>1p</sup>, R<sup>2p</sup>, R<sup>3p</sup>, R<sup>4p</sup>, R<sup>5p</sup>, R<sup>61b</sup>, R<sup>71a</sup>, s, X and Y have the earlier defined significations]

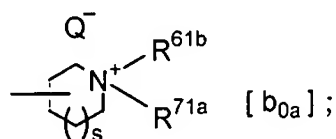
and if necessary removing the protective group(s) and/or exchanging the anion, a compound of the general formula [I-3]:

10



[in which A<sup>ba</sup> signifies a group expressed by the formula [b<sub>0a</sub>]

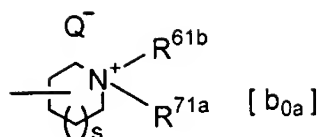
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Ar<sup>1</sup>, Ar<sup>2</sup>, Ar<sup>3</sup>, k, m, n, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>61b</sup>, R<sup>71a</sup>, s, X, Y and Q<sup>-</sup> have the earlier defined significations]

20 can be produced.

The production process 4 is a method for producing, among the compounds of the present invention represented by the general formula [I], those in which A is a group expressed by the formula [b<sub>0a</sub>]:



[in which  $\text{R}^{61b}$ ,  $\text{R}^{71a}$ ,  $s$  and  $\text{Q}^-$  have the earlier defined significations],

5 i.e., the compounds represented by the general formula [I-3].

As the "leaving group" expressed by  $\text{L}^2$ , those leaving groups exemplified as  $\text{L}^1$  in the production process 3 are equally applicable.

In the above reaction where such groups as oxo, hydroxyl, amino or imino which do not participate in the reaction are present in  
 10 the reactants, it is desirable to suitably protect them with protective groups of oxo, hydroxyl, amino or imino, respectively, before the reaction and to remove the protective groups ~~after the~~ after the reaction.

As the protective groups suitable for oxo, hydroxyl, amino or  
 15 imino, those respective protective groups as described in relation to the production process 1 are applicable as they are.

The reaction of a compound expressed by the general formula [VI-2] or salt thereof with a compound of the general formula [IV-1b] or salt thereof is usually carried out using a mol or molar excess,  
 20 preferably a large molar excess, of the compound of formula [VI-2] or salt thereof, per mol of the compound of the formula [IV-1b] or salt thereof, in the absence of a solvent or in an inert solvent which is not detrimental to the reaction, non-use of solvent being preferred.

As such inert solvent, for example, ethers such as diethyl  
 25 ether, tetrahydrofuran and dioxane; aromatic hydrocarbons such as benzene, toluene, chlorobenzene and xylene; halogenated hydrocarbons such as chloroform, dichloromethane and dichloroethane; and aprotic polar solvents such as dimethyl sulfoxide, N,N-dimethylformamide, acetonitrile and hexamethylphosphoric triamide; or mixtures  
 30 of the foregoing can be used, in particular, chloroform and acetonitrile being preferred.

For smooth progress, the reaction may be carried out in the presence of base and/or a reaction assistant.

As the base, for example, alkali metal bicarbonates such as sodium hydrogencarbonate and potassium hydrogencarbonate; alkali  
5 metal carbonates such as sodium carbonate and potassium carbonate; tertiary aliphatic amines such as trimethylamine, diethylamine, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]-  
10 non-5-ene (DBN); and aromatic amines such as pyridine, 4-dimethylaminopyridine, picoline, lutidine, quinoline and isoquinoline can be used. Of those, potassium carbonate, diethylamine, triethylamine and N,N-diisopropylethylamine are particularly suitable.

The use rate of the base is usually a mol or molar excess,  
15 preferably 1-3 mols, per mol of the compound of the formula [IV-1b].

As assistant useful for the reaction, for example, alkali metal iodides such as lithium iodide, sodium iodide and potassium iodide may be named. Of these, potassium iodide is preferred.

The use rate of the assistant is usually from catalytic to  
20 excessive amount, preferably from catalytic amount to one equivalent, to the compound of the formula [IV-1b].

The reaction temperature may usually range from about 0°C to the boiling point of the solvent or reagent used in the reaction, preferably from 20°C to the boiling point of the solvent or reagent  
25 used in the reaction, and the reaction time may usually range from 10 minutes to 48 hours, preferably 1-10 hours.

Upon completion of the reaction, after removing the protective groups in the compound of the general formula [IV-2] where they are present; or where no protective group is present in the  
30 product, without such an intervening treatment, the product is processed in the usual manner to produce a compound of the general formula [I-3].

For removing the protective groups and conducting the

post-treatment, those methods as described as to the production process 1 are applicable.

~~Those compounds~~ Those compounds of the general formula [I-3] are isolated as those having a certain or more than one kind of anions, and ~~thereafter the~~ thereafter the anions can be changed to other desired anions.

As the method of changing anions, for example, one comprising adsorbing the formula [I-3] compound onto a column filled with an adequate carrier, treating the same with a salt of an acid having an excess of desired anions, and eluting the intended formula [I-3] compound as formed.

#### Production process 5

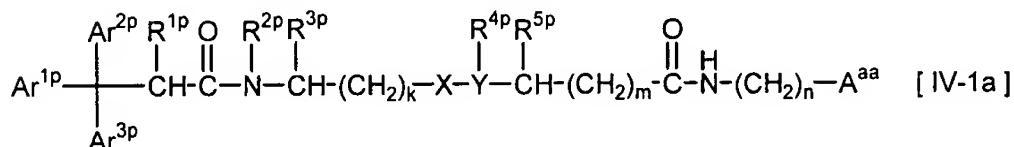
By following the steps of reacting a compound of the general formula [VII]:

15



[in which  $L^3$  and  $L^4$  each independently signifies a leaving group, and  $R^{71bp}$  signifies optionally substituted trimethylene, tetramethylene, 2-butenylene, pentamethylene, 3-oxapentamethylene or 2,3-epoxytetramethylene, the substituent being selected from the group consisting of lower alkyl, lower alkoxy, and optionally protected oxo and hydroxyl] or a salt thereof with a compound of a general formula [IV-1a]

25



[in which  $A^{aa}$ ,  $Ar^{1p}$ ,  $Ar^{2p}$ ,  $Ar^{3p}$ ,  $k$ ,  $m$ ,  $n$ ,  $R^{1p}$ ,  $R^{2p}$ ,  $R^{3p}$ ,  $R^{4p}$ ,  $R^{5p}$ ,  $s$ ,  $X$  and  $Y$  have the earlier defined significations] or a salt thereof, to form a compound of the general formula [IV-3]

30



significations],  
i.e., the compounds represented by the general formula [I-4].

As the "leaving group" expressed by  $L^3$  or  $L^4$ , those exemplified as  $L^1$  in the production process 3 are applicable  
5 independently of each other.

In the above reaction where such groups as oxo, hydroxyl, amino or imino which do not participate in the reaction are present in the reactants, it is desirable to suitably protect them with protective groups of oxo, hydroxyl, amino or imino, respectively, before the  
10 reaction and to remove the protective groups ~~after~~after the reaction.

As the protective groups suitable for oxo, hydroxyl, amino or imino, those respective protective groups as described in relation to the production process 1 are applicable as they are.

15 The reaction of a compound expressed by the general formula [IV-1a] or salt thereof with a compound of the general formula [VII] or salt thereof is usually carried out using a mol or molar excess, preferably 1-5 mols, of the compound of the formula [VII] or salt thereof, per mol of the compound of the formula [IV-1a] or salt thereof,  
20 in an inert solvent which is not detrimental to the reaction.

As such inert solvent, for example, ethers such as diethyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons such as benzene, toluene, chlorobenzene and xylene; halogenated hydrocarbons such as chloroform, dichloromethane and  
25 dichloroethane; and aprotic polar solvents such as dimethyl sulfoxide, N,N-dimethylformamide, acetonitrile and hexamethylphosphoric triamide; or mixtures of the foregoing can be used, among which chloroform and acetonitrile are preferred.

For smooth progress, the reaction may be carried out in the  
30 presence of base and/or a reaction assistant.

As the base, for example, alkali metal bicarbonates such as sodium hydrogencarbonate and potassium hydrogencarbonate; alkali metal carbonates such as sodium carbonate and potassium carbonate;

tertiary aliphatic amines such as trimethylamine, diethylamine, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo-  
5 [4.3.0]non-5-ene (DBN); and aromatic amines such as pyridine, 4-dimethylaminopyridine, picoline, lutidine, quinoline and isoquinoline can be used. Of those, potassium carbonate, diethylamine, triethylamine and N,N-diisopropylethylamine are preferred.

The use rate of the base is usually a mol or molar excess,  
10 preferably 1-3 mols, per mol of the compound of the formula [IV-1a].

As assistant useful for the reaction, for example, alkali metal iodides such as lithium iodide, sodium iodide and potassium iodide may be named. Of these, potassium iodide is preferred.

The use rate of the assistant is usually from catalytic to  
15 excessive amount, preferably from catalytic amount to one equivalent, to the compound of the formula [IV-1a].

The reaction temperature may usually range from about 0°C to the boiling point of the solvent or reagent which is used in the reaction, preferably from 20°C to the solvent or reagent used in the  
20 reaction, and the reaction time may usually range from 10 minutes to 48 hours, preferably 1-10 hours.

Upon completion of the reaction, after removing the protective groups in the compound of the general formula [IV-3] where they are present; or where no protective group is present in the  
25 product, without such an intervening treatment, the product is processed in the usual manner or if necessary exchanged of the anions therein to produce a compound of the general formula [I-4].

For removing the protective groups and other post-treatments, those methods as described in the explanation of the production process 1 are applicable as they are, and for changing  
30 anions, the method as described as to above production process 4 is applicable as it is.

Isolation and purification of ~~these compounds~~ those

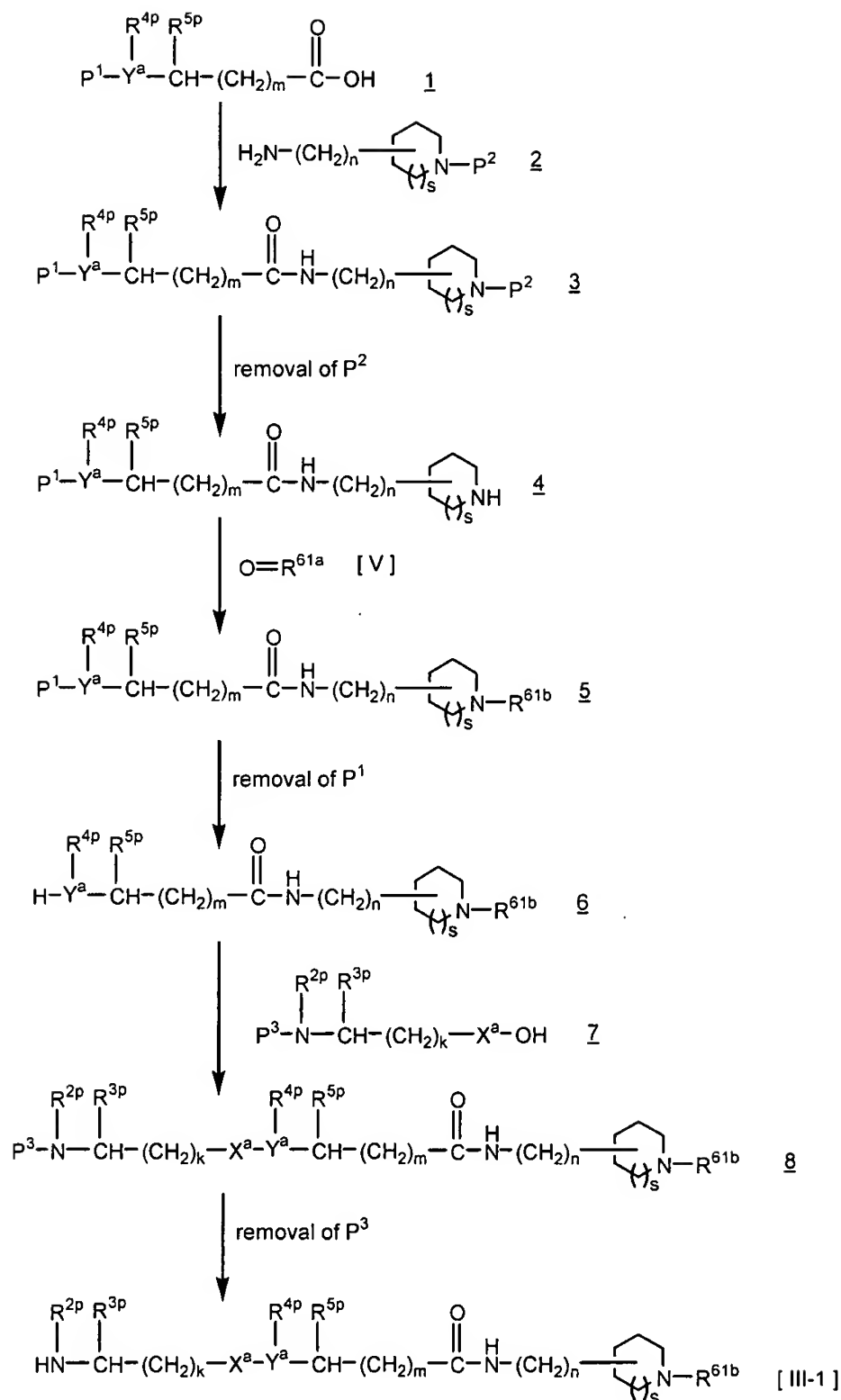


compounds of the general formulae [I-1], [I-2], [I-3] or [I-4] which are obtained in above processes can be accomplished by customarily practiced separation means such as column chromatography using silica gel, adsorptive resins and the like, thin-layer chromatography, liquid chromatography, solvent extraction or recrystallization-reprecipitation, applied singly or in combination.

Compounds of the general formula [I-1] or [I-2] are convertible to pharmaceutically acceptable salts by customary means and conversely, conversion from the salts to free compounds can also be conducted following customary means.

As ~~these compounds~~ those compounds represented by general formulae [II], [III], [IV-1a], [V], [VI-1], [VI-2] or [VII], commercial products may be used, or they can be prepared by methods which are described in literature references (cf. M. Bodansky and M.A. Ondetti, Peptide Synthesis, Interscience, New York, 1966; F.M. Finn and K. Hofmann, The Proteins, Vol. 2, ed. by H. Nenrath and R. L. Hill, Academic Press Inc., New York, 1976; Nobuo Izumiya, et al., Peptide Gosei (synthesis), Maruzen Co., 1975; and Official Patent KOKAI (laid-open) Gazette, KOKAI No. Sho 62(1987)-215588), methods analogous to the above, methods described in the following or those used in working and referential examples given in this specification.

Production method A



[in the above formulae, P<sup>1</sup> and P<sup>3</sup> signify protective groups of amino or imino group; P<sup>2</sup> signifies a protective group of imino group; X<sup>a</sup> signifies carbonyl group; Y<sup>a</sup> signifies nitrogen atom; and k, m, n, R<sup>2p</sup>, R<sup>3p</sup>, R<sup>4p</sup>, R<sup>5p</sup>, R<sup>61a</sup>, R<sup>61b</sup> and s have the earlier defined significations].

This production method is that for producing the compounds represented by the general formula [III-1], according to which the compounds of the general formula [III-1] can be produced by the steps of having a compound of the general formula 2 act on a compound of the general formula 1 to form a compound of the general formula 3; removing therefrom the protective group P<sup>2</sup> to form a compound 4 on which a compound of the general formula [V] is acted to form a compound of the general formula 5; removing therefrom the protective group P<sup>1</sup> to form a compound 6 on which a compound of the general formula 7 is acted to form a compound of the general formula 8; and finally removing therefrom the protective group P<sup>3</sup>.

The step of preparing a compound 3 from a compound 1 and that of preparing a compound 3 from a compound 1 can each be conducted similarly to the step in the production process 1 of reacting a carboxylic acid of the general formula [II] or salt or reactive derivative thereof with a compound of the general formula [III] or salt thereof, and hence the reaction conditions earlier described about the reaction can be applied.

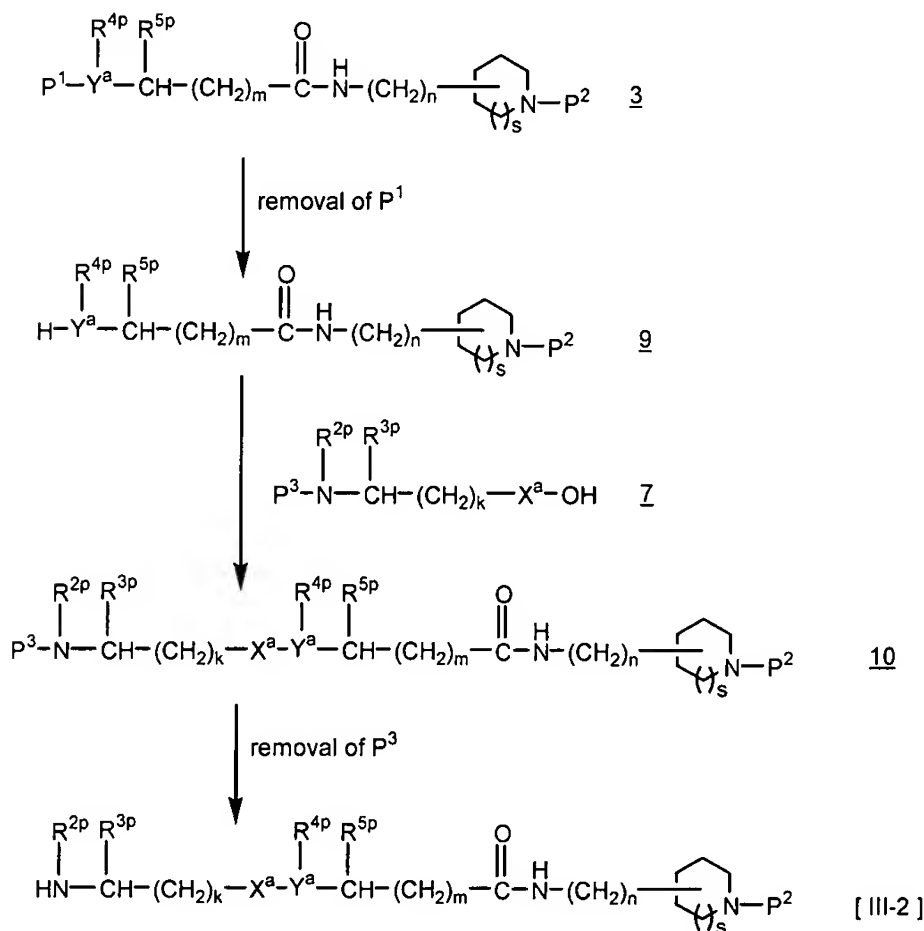
As examples of the protective groups P<sup>1</sup>, P<sup>2</sup> or P<sup>3</sup> for amino or imino group, those used as to the production process 1 can be named.

Steps for removing said protective groups can each be conducted following those methods taught in the literature references cited in respect of said production process 1.

The step of producing a compound 5 from a compound 4 can be conducted in the manner similar to the step of reacting a compound of the general formula [IV-1a] or salt thereof with a compound of the general formula [V] in the production process 2, and hence similar conditions are applicable as the reaction conditions.

Furthermore, as ~~those compounds~~ those compounds expressed by the general formulae 1, 2 or 7, either ~~those chemicals~~ those chemicals on the market may be used or they may be prepared according to known processes, those described in the working or  
 5 referential examples given in this specification or those analogous thereto, if necessary in suitable combinations.

Production method B



10

[in which k, m, n, P<sup>1</sup>, P<sup>2</sup>, P<sup>3</sup>, R<sup>2p</sup>, R<sup>3p</sup>, R<sup>4p</sup>, R<sup>5p</sup>, s, X<sup>a</sup> and Y<sup>a</sup> have the earlier defined significations].

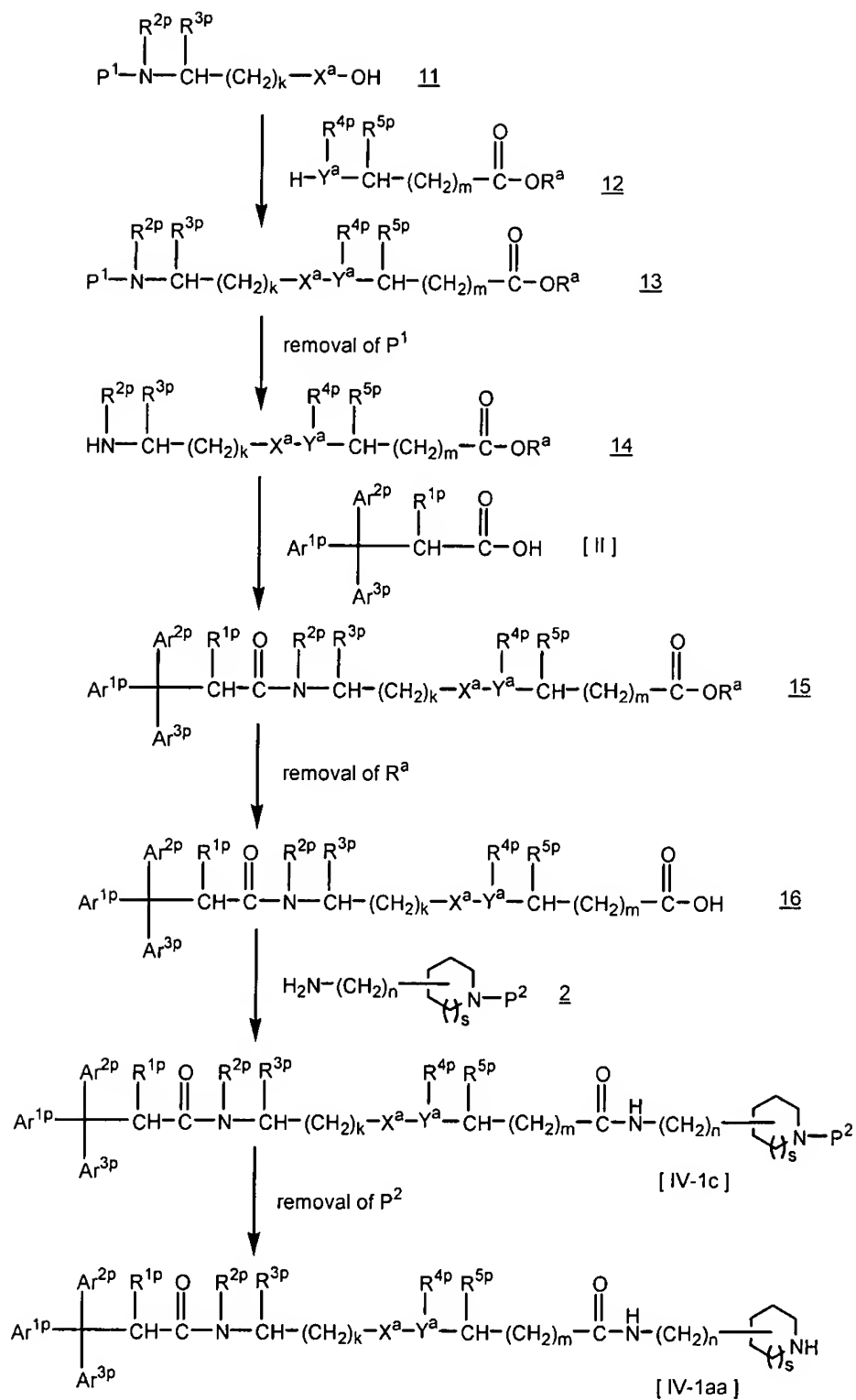
This production method is that for preparing the compounds represented by the general formula [III-2]. According to this method,  
 15 the compounds of the general formula [III-2] can be produced by the

steps of converting a compound of the general formula 3 to one of the  
general formula 9 by removing the protective group P<sup>1</sup> from the  
former; having a compound of the general formula 7 act on said  
compound 9 to form a compound of the general formula 10; and finally  
5 removing the protective group P<sup>3</sup> from said compound 10.

The step of preparing a compound 10 from a compound 9 can  
be conducted similarly to the step in the production process 1 of  
reacting a carboxylic acid of the general formula [II] or salt or reactive  
derivative thereof with a compound of the general formula [III] or salt  
10 thereof, and hence the reaction conditions earlier described about the  
reaction can be applied.

Steps for removing the protective groups of amino or imino,  
which are expressed as P<sup>1</sup> or P<sup>3</sup> can each be conducted following those  
methods taught in the literature references cited in respect of said  
15 production process 1.

#### Production method C



[in which R<sup>a</sup> stands for lower alkyl; and Ar<sup>1p</sup>, Ar<sup>2p</sup>, Ar<sup>3p</sup>, k, m, n, P<sup>1</sup>, P<sup>2</sup>, R<sup>1p</sup>, R<sup>2p</sup>, R<sup>3p</sup>, R<sup>4p</sup>, R<sup>5p</sup>, s, X<sup>a</sup> and Y<sup>a</sup> have the earlier defined significations]

This production method is that for producing the compounds  
5 represented by the general formula [IV-1aa], according to which the compounds of the general formula [IV-1aa] can be produced by the steps of having a compound of the general formula 12 act on a compound of the general formula 11 to form a compound of the general formula 13; removing therefrom the protective group P<sup>1</sup> to  
10 form a compound 14 on which a compound of the general formula [II] is acted to form a compound of the general formula 15; removing therefrom the lower alkyl R<sup>a</sup> to form a compound 16 on which a compound of the general formula 2 is acted to form a compound of the general formula [IV-1c]; and finally removing therefrom the protective  
15 group P<sup>2</sup>.

The step of preparing a compound 13 from a compound 11, that of preparing a compound 15 from a compound 14 and that of preparing a compound [IV-1c] from a compound 16 can each be conducted similarly to the step in the production process 1 of reacting  
20 a carboxylic acid of the general formula [II] or salt or reactive derivative thereof with a compound of the general formula [III] or salt thereof, and hence the reaction conditions earlier described about the reaction can be applied.

Steps for removing said protective groups of amino or imino, which are expressed as P<sup>1</sup> or P<sup>2</sup>, and for removing the lower alkyl expressed as R<sup>a</sup> can each be conducted following those methods taught in the literature references cited in respect of said production  
25 process 1.

Furthermore, as ~~these compounds~~ those compounds  
30 expressed by the general formulae 11 or 12, either ~~these chemicals~~ those chemicals on the market may be used or they may be prepared according to known processes, those described in the working or referential examples given in this specification or those analogous

thereto, if necessary in suitable combinations.

Utility of ~~these compounds~~ those compounds of the present invention is demonstrated by the following results of the tests on inhibition of binding to muscarinic receptors and those on antagonism  
5 against various muscarinic receptors.

Tests on inhibition of binding to muscarinic receptors

These tests were performed according to a modification of the method of Hargreaves, et al. (Br. J. Pharmacol. 107: 494-501, 1992). Namely, muscarinic acetylcholine receptors of human m<sub>1</sub>, m<sub>2</sub>,  
10 m<sub>3</sub>, m<sub>4</sub> and m<sub>5</sub> expressed in CHO cells (Receptor Biology, Inc.) were incubated with 0.2 nM [<sup>3</sup>H]-N-methylscopolamine (82Ci/mmol, New England Nuclear, Inc.) and a test compound to be tested in 0.5 ml of 50 mM Tris-HCl, 10 mM MgCl<sub>2</sub>, 1 mM EDTA solution (pH 7.4) for 120 minutes at room temperature (about 20-25°C), followed by  
15 suction filtration over a glass filter (UniFilter plate-GF/C; Packard). Then the filter was washed four times with 1 ml of ice-cold Tris-HCl buffer and dried at 50°C for an hour. After adding a scintillator (Microscinti 0; Packard), the radioactivity of [<sup>3</sup>H]-N-methylscopolamine binding to the filter was counted with a microplate  
20 scintillation counter (TopCount™; Packard). Non-specific receptor binding of [<sup>3</sup>H]-N-methylscopolamine was measured by adding 1μM N-methylscopolamine. According to the method of Cheng and Prusoff (Biochem. Pharmacol. 22: 3099-3108, 1973), the binding affinity of a compound of the present invention for muscarinic  
25 receptors is expressed by dissociation constant (K<sub>i</sub>) which is calculated from the concentration (IC<sub>50</sub>) of the test compound which achieves 50% inhibition of binding of [<sup>3</sup>H]-N-methylscopolamine, the labeled ligand. The results are shown in Tables 1-1 and 1-2.



TABLE 1-1

Inhibitory Effects on Binding to Muscarinic  
m<sub>1</sub>, m<sub>2</sub>, m<sub>3</sub>, m<sub>4</sub> and m<sub>5</sub> Receptors

5

Compound	Ki(nM)					Selectivity (times)			
	m <sub>1</sub>	m <sub>2</sub>	m <sub>3</sub>	m <sub>4</sub>	m <sub>5</sub>	m <sub>1</sub> /m <sub>3</sub>	m <sub>2</sub> /m <sub>3</sub>	m <sub>4</sub> /m <sub>3</sub>	m <sub>5</sub> /m <sub>3</sub>
Example 6	860	250	1.8	66	82	480	140	37	46
Example 12	140	34	0.38	18	32	370	89	47	84
Example 19	270	30	0.75	8.1	19	360	40	11	25
Example 28	130	85	1.2	36	220	110	71	30	180

TABLE 1-2

Inhibitory Effects on Binding to Muscarinic  
m<sub>1</sub>, m<sub>2</sub>, m<sub>3</sub>, m<sub>4</sub> and m<sub>5</sub> Receptors

10

Compound	Ki(nM)					Selectivity (times)			
	m <sub>1</sub>	m <sub>2</sub>	m <sub>3</sub>	m <sub>4</sub>	m <sub>5</sub>	m <sub>1</sub> /m <sub>3</sub>	m <sub>2</sub> /m <sub>3</sub>	m <sub>4</sub> /m <sub>3</sub>	m <sub>5</sub> /m <sub>3</sub>
Example 133	>2500	810	3.2	140	1600	>780	250	44	500
Example 144	110	110	1.3	27	230	85	85	21	180
Example 146	1200	1000	15	360	490	80	67	24	33
Example 150	150	490	4.7	310	850	32	100	66	180
Example 151	450	460	3.5	74	890	130	130	21	250

As is clear from the results indicated in above Tables 1-1 and 1-2, ~~these compounds~~ those compounds of the present invention exhibited far higher binding-inhibitory activity to m<sub>3</sub> receptor, than to m<sub>1</sub>, m<sub>2</sub>, m<sub>4</sub> and m<sub>5</sub> receptors.

Tests for antagonism to muscarinic receptors (in vitro)

1) Test for antagonism to M<sub>2</sub> receptor in isolated rat right atrium

The test was performed according to a conventional method.

20

Male SD strain rats (weighing 300-500 g) were killed by exsanguination, and from each of them the right atrium was isolated. Each preparation was isometrically suspended in a Magnus tube filled with 20 ml of Krebs-Henseleit solution (gassed with 95% O<sub>2</sub> - 5% CO<sub>2</sub> and kept at 32°C) with an initial tension of 0.5 g. The heart rate was recorded with a heart rate counter. ~~After the~~ After the preparation was equilibrated for 30 minutes, carbachol (10<sup>-9</sup> to 10<sup>-6</sup> M) was cumulatively administered from a low concentration to three-fold increasing doses and accompanying decrease in heart rate was measured to obtain a dose-response curve for the control experiment. ~~After the~~ After the preparation was washed with fresh solution to restore the heart rate, a test compound was administered thereto. Ten minutes later, carbachol was cumulatively administered again. Responses to carbachol were expressed as percentages based on the heart rate before administration of carbachol as 100%. The antagonistic potency (K<sub>B</sub> value) of the test compound was determined from the degree of shift of the dose-~~[[response curve]]~~ response curve attributable to the treatment with individual test compound of the present invention. The results were as shown in Tables 2-1 and 2-2.

## 20                    2) Test for antagonism to the airway M<sub>3</sub> receptor in isolated rat trachea

The test was performed according to a conventional method. Male SD strain rats (weighing 300-500 g) were killed by exsanguination, and from each of them the trachea was isolated. Annular segments (2 mm wide) were cut out from the trachea and cut transversely at the anterior cartilage part to make open ring preparation. Each preparation was suspended in a Magnus tube filled with 5 ml of Krebs-Henseleit solution (gassed with 95% O<sub>2</sub> - 5% CO<sub>2</sub> and kept at 32°C) with an initial tension of 1.0 g and a resting tension of 0.6 g. The tension of the preparation was recorded isometrically. After being equilibrated for an hour, the preparation was made to contract twice by treatment with 10<sup>-4</sup> M carbachol, and the second contraction induced by carbachol was used as the reference

contraction. After washing the preparation with fresh solution to restore it to the base line, a test compound was administered thereto (or no treatment was given). Ten minutes later, carbachol ( $10^{-8}$  to  $10^{-3}$  M) was cumulatively administered in three-fold increasing doses to obtain a dose-response curve. The dose-response curve was plotted by expressing responses as percentages based on the reference contraction of the preparation as 100%. The antagonistic potency ( $K_B$  value) of the test compound was determined from the degree of shift of the dose-response curve attributable to the treatment with the test compound. The results were as shown in Tables 2-1 and 2-2.

TABLE 2-1  
Antagonism to Muscarinic Receptors (in vitro)

Compound	$K_B$ (nM)		Selectivity (times)
	Right Atrium $M_2$	Trachea $M_3$	$M_2/M_3$
Example 12	160	2.3	70

TABLE 2-2  
Antagonism to Muscarinic Receptors (in vitro)

Compound	$K_B$ (nM)		Selectivity (times)
	Right Atrium $M_2$	Trachea $M_3$	$M_2/M_3$
Example 133	41	0.71	58

As is clear from the results indicated in above Tables 2-1 and 2-2, the compounds of the present invention exhibited far more powerful antagonism to the trachea  $M_3$  receptor than to the right atrium  $M_2$  receptor. Therefore, the compounds of the present invention are more selective for trachea  $M_3$  receptor.

Tests for antagonism against muscarinic receptors (in vivo)

1) Test for antagonism to M<sub>1</sub> receptor (inhibitory effects on McNeil-A-343-induced vasopressor reaction in cervical vertebrae-separated rats)

5 Male SD strain rats (weighing 300-500g) were anesthetized with intraperitoneal administration of pentobarbital (50 mg/kg). Each rat's airway was cannulated by laryngotomy. Also by femoral incision, femoral artery and vein were isolated each and cannulated, which were used as routes for heart rate counting and chemical  
10 administration, respectively. Using a pulmotor for small animals (Type 7025, Ugo Basile Co.), artificial respiration was conducted under the conditions of ventilation rate of 6 ml/kg per breath and respiration rate of 90 breaths/min. The heart rate and blood pressure variations were measured with a heart rate counter (AT-601  
15 G, Nippon Kodon Co.) and a tonometer (AP-641G, Nippon Kodon Co.), via a pressure transducer (DX-312, Nippon Kodon Co.). ~~After the~~ After the blood pressure was stabilized, the cervical vertebrae was separated with an injection needle pricked from the occipital region. ~~After the~~ After the average blood pressure dropped to not higher than  
20 70 mmHg, test compound (test compound-treated group) or isotonic sodium chloride solution (control group) was intravenously administered. Five (5) minutes thereafter, McNeil-A-343 (0.3 mg/kg) was intravenously administered, and whereby induced hypertension variation was recorded. In this experiment one-dose evaluation per  
25 one animal was conducted. The inhibitory effect (inhibition ratio) of the test compound on the McNeil-A-343-induced vasopressor reaction was determined by the following equation:

30 Inhibition ratio (%) =

$$\left(1 - \frac{\text{blood pressure variation in test compound-treated group}}{\text{blood pressure variation in control group}}\right) \times 100$$

The 50% inhibition dose ( $ED_{50}$ ;  $\mu\text{g/kg}$ ) was calculated from the inhibition ratio of each dose of the tested compound. The results were as shown in Tables 3-1 and 3-2 as the antagonism to  $M_1$  receptor of the tested compounds.

5

2) Test for antagonism to  $M_2$  receptor (inhibitory effects to acetylcholine-induced bradycardia reaction in rats)

Male SD strain rats (weighing 300-500 g) were anesthetized with urethane (1g/kg) and  $\alpha$ -chloralose (50 mg/kg) administered intraperitoneally. The airway, carotid artery and vein of each rat were isolated by laryngotomy and cannulated. The carotid artery and vein cannulae were made the routes for heart rate counting and drug administration. After suppressing the rats' spontaneous respiration by hypodermic administration of succinylcholine (5 mg/body), artificial ventilation was conducted under the conditions of ventilation rate of 6 ml/kg per breath and respiration rate of 90 breaths/min., using a pulmotor for small animals (Model 681, Harvard Co.). The variations in heart rate and blood pressure were measured with a heart rate counter (AP-601G, Nippon Kodon Co.) and a tonometer (AP-641G, Nippon Kodon Co.), via a pressure transducer (DX-312, Nippon Kodon Co.). After about 10 minutes' stabilization period, heart rate change was induced by intravenous administration of acetylcholine (10 $\mu\text{g/kg}$ ), and the mean value of the change was recorded as the value before the drug administration (pre-value) of the body. After calculating the pre-values, the test compound (test compound-treated group) or isotonic sodium chloride solution (control group) was intravenously administered. Five minutes thereafter, acetylcholine was intravenously administered and whereby induced change in the heart rate was recorded. In this experiment, one-dosage evaluation was conducted per one animal of the tested rats. The change in acetylcholine-induced bradycardia reaction (% of pre-value) caused by the test compound and isotonic sodium chloride solution was determined by the following Equation 1:

Equation 1:

$$\begin{aligned} &\text{Percent of pre-value} = \\ &\quad \frac{\text{heart rate change after administration of test compound} \\ &\quad \text{(isotonic sodium chloride solution)}}{\text{heart rate change before administration (pre-value) of} \\ &\quad \text{test compound (isotonic sodium chloride solution)}} \times 100 \end{aligned}$$

10            The inhibitory effect (inhibition ratio) of each test compound on the acetylcholine-induced bradycardia reaction was determined according to the following Equation 2:

Equation 2:

$$\begin{aligned} 15 \quad &\text{Inhibition ratio (\%)} = \\ &\quad \frac{\% \text{ of pre-value (test compound-treated group)}}{(1 - \frac{\% \text{ of pre-value (test compound-treated group)}}{\% \text{ of pre-value (control group)}}) \times 100} \end{aligned}$$

20            Fifty (50%) inhibition dose (ED<sub>50</sub>; µg/kg) was calculated from the inhibition ratio of each dose of the tested compound. The results were as shown in Tables 3-1 and 3-2 as the antagonism to M<sub>2</sub> receptor of tested compounds.

25    3)    Test for antagonism to muscarinic M<sub>3</sub> receptor (inhibitory effects on acetylcholine-induced airway resistance-increasing reaction in rats)

30            Male SD strain rats (weighing 300-500 g) were anesthetized with urethane (1 g/kg) and α-chloralose (50 mg/kg) administered intraperitoneally. The airway and carotid artery of each rat were isolated by laryngotomy and cannulated. The carotid artery cannula was used as the test compound administration route. After suppressing spontaneous respiration by hypodermic administration of

succinylcholine (5 mg/body), the rats were transferred into Plethysmograph-box (PLYAN, Buxco) and artificially ventilated under the conditions of ventilation rate of 6 ml/kg per breath and respiration rate of 90 breaths/min., using a pulmotor for small animals (Model 5 681, Harvard Co.). Measurements of air rate and intracellular pressure, calculation of airway resistance and lung compliance and their recording were conducted with lung function analyzer (Model 6, Buxco). After about 10 minutes' stabilization period, the change in airway resistance induced by intravenous administration of 10 acetylcholine (50 µg/kg) was measured twice at 5 minutes' interval. The change in airway resistance induced by the second acetylcholine administration was recorded as the pre-administration of the tested rat (pre-value). Five (5) minutes ~~after the~~ after the second acetylcholine-induced reaction measurement, the test compound or 15 isotonic sodium chloride solution was intravenously administered. Five (5) minutes thereafter, acetylcholine was administered and whereby induced airway resistance change was measured. In this experiment, one-dosage evaluation was conducted per one animal of the tested rats. The changes in acetylcholine-induced airway 20 resistance-increasing reaction.(% of pre-value) caused by the tested compound and isotonic sodium chloride solution were calculated by the following Equation 1:

Equation 1:

$$\begin{aligned}
 & \text{Percent of pre-value} = \\
 & \quad \frac{\text{change in airway resistance after administration of test} \\
 & \quad \text{compound (isotonic sodium chloride solution)}}{\text{change in airway resistance before administration of} \\
 & \quad \text{test compound (isotonic sodium chloride solution)}} \times 100
 \end{aligned}$$

The inhibitory effect (inhibition ratio) of each test compound on the acetylcholine-induced airway resistance-increasing reaction

was determined according to the following Equation 2.

Equation 2:

$$\text{Inhibition ratio (\%)} = \left( 1 - \frac{\% \text{ of pre-value (test compound-treated group)}}{\% \text{ of pre-value (control group)}} \right) \times 100$$

Fifty (50)% inhibition dose (ED<sub>50</sub>; µg/kg) was calculated from the inhibition ratio of each dose of the tested compound. The results were as shown in Tables 3-1 and 3-2 as the antagonism to M<sub>3</sub> receptor of the tested compounds.

TABLE 3-1

Antagonism to Muscarinic Receptors (in vivo)

Compound	ED <sub>50</sub> (µg/kg, i.v.)			Selectivity (times)	
	vasopressor M <sub>1</sub>	bradycardia M <sub>2</sub>	Airway constriction M <sub>3</sub>	M <sub>1</sub> /M <sub>3</sub>	M <sub>2</sub> /M <sub>3</sub>
Example 12	>3000	1550	15	>200	100
atropine	19	5.2	4.3	4.4	1.2



TABLE 3-2  
Antagonism to Muscarinic Receptors (in vivo)

Compound	ED <sub>50</sub> (μg/kg, i.v.)			Selectivity (times)	
	vasopressor M <sub>1</sub>	bradycardia M <sub>2</sub>	Airway constriction M <sub>3</sub>	M <sub>1</sub> /M <sub>3</sub>	M <sub>2</sub> /M <sub>3</sub>
Example 133	>300	114	2.1	>143	54
<del>atropine-</del> <u>atropine</u>	19	5.2	4.3	4.4	1.2

5

As is clear from the results as shown in above Tables 3-1 and 3-2, the compounds of the present invention exhibited high M<sub>3</sub> selectivity also in vivo.

10

4) Test for antagonism to M<sub>3</sub> receptor (bronchodilation in anesthetized dogs)

The bronchodilation action of inhaled test compound was evaluated by measuring the compounds' inhibitory action on  
 15 respiratory resistance-increasing reaction induced by a methacholine provocation test. For the experiment, 12 to 36 months old male beagle dogs (weighing 10-15 kg) were used. After being anesthetized by intravenous pentobarbital administration (30 mg/kg), the dogs were intubated cannulae in their trachea. ~~After their~~ After their  
 20 respiration became stable, the cannulae were connected with Astograph (TCK-6100H, Chest) and a methacholine provocation test by 3Hz oscillation method was conducted. The inhaling inducer, methacholine, was diluted with isotonic sodium chloride solution in 10-grade concentration levels starting from 40,000 μg/ml, successively  
 25 as 20,000 to 10,000, 5,000, 2500, 1250, 625, 312.5, 156 and 78 μg/ml. The dogs were caused to inhale these methacholine solutions each for one minute starting from the one of low concentration with the

nebulizer in the Astograph, and changes in respiratory resistance were continuously plotted. The methacholine concentration at which the respiratory resistance increased to twice the initial value was recorded as the methacholine reaction threshold value. Before evaluating the test compounds, the methacholine reaction threshold value<sup>1)</sup> under no drug treatment was measured at least twice at a week's interval, to select the dogs showing reproducible reaction.

The inhaling administration of each test compound (1 mg/ml) was conducted for 10 minutes under pentobarbital anesthetization (30 mg/kg, i.v.), with the nebulizer in the Astograph. Thereafter pentobarbital was additionally administered when necessary, to maintain the anesthetized condition. Four hours ~~after~~after the administration, a methacholine provocation test was conducted, to measure the methacholine reaction threshold value<sup>2)</sup> after administration of each test compound. The bronchodilator activity (shift value) of each tested compound was determined according to the following equation:

$$\text{Shift value} = \frac{\text{methacholine reaction threshold value}^{1)}}{\text{after drug administration}}$$


---


$$\text{methacholine reaction threshold value}^{2)}$$

without drug administration

TABLE 4  
Antagonism to Muscarinic Receptor  
(in vivo: Anesthetized Dogs)

Compound	Shift (fold)
	Airway constriction $M_3$
Example 133	20.2
Example 151	>40.0

As is clearly demonstrated in above Table 4, the compounds of the present invention exhibited powerful bronchodilation action and long duration of the action.

As above, the compounds of formula [I] of the present invention exhibit potent and selective antagonistic activity against muscarinic  $M_3$  receptor. Hence, they can be administered to patients orally or parenterally as safe pharmaceuticals exhibiting little side effects, for treating, in particular, such respiratory diseases as chronic obstructive pulmonary diseases, chronic bronchitis, asthma, chronic respiratory tract obstruction, fibroid lung, pulmonary emphysema and rhinitis; digestive diseases such as irritable bowel syndrome, convulsive colitis, gastroduodenal ulcer, convulsion or hyperanakesia of digestive tract, diverticulitis and pain accompanying contraction of smooth muscles of the digestive system; urinary diseases accompanied by dysuria like urinary incontinence, urgency and pollakiuria in nervous pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis; and motion sickness.

For actual use of ~~these compounds~~ those compounds of the present invention for therapeutic treatment or prophylaxis of diseases as exemplified above, they may be combined with pharmaceutically acceptable adjuvants in the usual manner to formulate pharmaceutical preparations of forms suitable for administration. For this purpose, there can be used a variety of adjuvants which are commonly used in the field of pharmaceuticals. Such adjuvants include, for example, gelatin, lactose, sucrose, titanium oxide, starch,

crystalline cellulose,  
~~hydroxypropylmethylcellulose, carboxymethylcellulose, corn starch,~~  
hydroxypropylmethylcellulose, carboxymethylcellulose, corn starch,  
microcrystalline wax, white petrolatum, magnesium aluminate  
5 metasilicate, anhydrous calcium phosphate, citric acid, trisodium  
citrate, hydroxypropyl cellulose, sorbitol, sorbitan fatty acid ester,  
polysorbate, sucrose fatty acid ester, polyoxyethylene, hardened  
castor oil, polyvinylpyrrolidone, magnesium stearate, light anhydrous  
silicic acid, talc, vegetable oil, benzyl alcohol, gum arabic, propylene  
10 glycol, polyalkylene glycol, cyclodextrin and hydroxy-  
propylcyclodextrin.

The dosage forms of pharmaceutical preparations formulated  
using these adjuvants include solid preparations such as tablets,  
capsules, granules, powders and suppositories; and liquid  
15 preparations such as syrups, elixirs and injections. These  
preparations may be formulated according to conventional techniques  
well-known in the field of pharmaceuticals. Liquid preparations may  
be in a form which is dissolved or suspended in water or other suitable  
medium prior to use. In particular, injections may be in the form of a  
20 solution or suspension in physiological saline solution or a glucose  
solution, or in powder form to be dissolved or suspended in  
physiological saline or a glucose solution prior to use. If desired,  
such injections may contain buffer agents and/or preservatives.

As preparations for oral administration, such formulation  
25 forms, besides ordinary tablets, capsules, granules, powders and the  
like, aerosols or dry powders for inhalation, elixiers or suspensions  
containing spices or coloring agents may be employed.

In these pharmaceutical preparations, a compound in  
accordance with the present invention may be present at a ratio of  
30 from 1.0 to 100% by weight, preferably 1.0 to 60% by weight, based on  
the total weight of individual preparation. These pharmaceutical  
preparations may additionally contain other therapeutically effective  
compounds.

When the compounds of the present invention are used as drugs, their dosage level and dosage schedule may vary according to the sex, age, body weight, severity of symptoms of individual patient, type and range of the desired therapeutic effect, and the like.

5 Generally for oral administration, they are preferably administered in a daily dose of 0.1 to 100 mg/kg for adults and this daily dose may be given at a time or in several divided doses. For parenteral administration, they are preferably administered in a daily dose of 0.001 to 10 mg/kg which may be given at a time or in several divided  
10 doses.

#### Optimum Embodiments for Practicing the Invention

~~Hereinafter the~~ Hereinafter the present invention is more specifically explained with reference to working examples, it being understood that the examples are in no way limitative of the scope of  
15 the invention.

#### Example 1

N-(2-{3-((3R)-1-(2-methylbutyl)-3-piperidyl)methyl}amino-3-oxopropyl)amino-2-oxoethyl)-3,3,3-triphenylpropanamide  
20 (Step 1)

Synthesis of ethyl 3-(2-((tert-butoxycarbonyl)amino)-acetylamino)propionate

To a solution of 1.5 g of ethyl 3-aminopropionate monohydrochloride and 1.7 g of 2-((tert-butoxycarbonyl)amino)acetic acid in 50  
25 ml of chloroform, 1.6 g of 1-hydroxybenzotriazole monohydrate, 2.3 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide monohydrochloride and 1.4 ml of triethylamine were added at room temperature by the order stated, and stirred for 2 hours at the same temperature. The reaction liquid was diluted with chloroform, and washed successively  
30 with saturated aqueous sodium bicarbonate solution, 10% aqueous citric acid solution and saturated saline solution, by the order stated, and dried on anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was

purified by means of silica gel column chromatography (eluting solvent: hexane/ethyl acetate = 1/4) to provide 2.0 g of the title compound.

(Step 2)

5            Synthesis of ethyl 3-((2-aminoacetyl)amino)propionate monohydrochloride

2.0 Grams of ethyl 3-(2-((tert-butoxycarbonyl)amino)-acetyl)amino)propionate were dissolved in 30 ml of 10% hydrochloric acid-methanol and stirred for 15 hours at room temperature. Upon  
10            distilling the reaction liquid off under reduced pressure, 1.52 g of the title compound was obtained.

(Step 3)

Synthesis of ethyl 3-(2-((3,3,3-triphenylpropanoyl)amino)-acetyl)amino)propionate

15            To a solution of 1.52 g of ethyl 3-((2-aminoacetyl)amino)propionate monohydrochloride and 2.18 g of 3,3,3-triphenylpropionic acid in 20 ml of chloroform, 1.46 g of 1-hydroxybenzotriazole monohydrate, 2.07 g of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide monohydrochloride and 2.0 ml of triethylamine were  
20            successively added at room temperature by the order stated, followed by 2 hours' stirring at the same temperature. The reaction liquid was diluted with ethyl acetate and washed successively with aqueous saturated sodium bicarbonate solution, 1N-hydrochloric acid and water, and filtered through cerite. The filtrate was dried on  
25            anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by means of silica gel column chromatography (eluting solvent: hexane/ethyl acetate = 4/1 — chloroform/methanol = 10/1) to provide 1.7 g of the title compound.

30            (Step 4)

Synthesis of 3-(2-((3,3,3-triphenylpropanoyl)amino)-acetyl)amino)propionic acid

1.7 Grams of ethyl 3-(2-((3,3,3-triphenylpropanoyl)amino)-

acetylamino)propionate was dissolved in a mixed liquid consisting of 70 ml of tetrahydrofuran and 20 ml of methanol. To the solution 5.0 ml of 4N aqueous sodium hydroxide solution was added at room temperature, followed by an hour's stirring at the same temperature.

5 The reaction liquid was distilled off under reduced pressure, and the residue was rendered acidic by addition of 1N hydrochloric acid, extracted with ethyl acetate, washed with saturated saline solution and dried over anhydrous magnesium sulfate. Upon distilling the solvent off under reduced pressure, 1.10 g of the title compound was

10 obtained.

(Step 5)

#### Synthesis of

N-(2-{3-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)amino-3-oxopropyl}amino-2-oxoethyl)-3,3,3-triphenylpropanamide

15 To a solution of 0.55 g of (3R)-3-aminomethyl-1-(tert-butoxycarbonyl)piperidine and 1.1 g of 3-(2-{(3,3,3-triphenylpropanoyl)amino}acetylamino)propionic acid in 10 ml of N,N-dimethylformamide, 0.52 g of 1-hydroxybenzotriazole monohydrate and 0.75 g of 1-ethyl-3-(3-dimethylaminopropyl)

20 carbodiimide monohydrochloride were successively added at room temperature, and stirred for 2 hours at the same temperature. Then 2.0 ml of triethylamine and 10 ml of chloroform were added at room temperature, followed by an hour's stirring at the same temperature. The reaction liquid was distilled off under reduced pressure, diluted

25 with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate solution, 10% aqueous citric acid solution and saturated saline solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure and the residue was purified by means of silica gel column chromatography

30 (eluting solvent: chloroform/methanol = 19/1) to provide 1.41 g of the title compound.

(Step 6)

Synthesis of N-(2-{3-(((3S)-3-piperidylmethyl)amino-3-

oxopropyl}amino-2-oxoethyl)-3,3,3-triphenylpropanamide  
monohydrochloride

Using N-(2-{3-(((3R)-1-(tert-butoxycarbonyl)-3-  
piperidyl)methyl)amino-3-oxopropyl}amino-2-oxoethyl)-3,3,3-  
5 triphenylpropanamide, the title compound was prepared by a method  
similar to Step 2 of Example 1.  
(Step 7)

Synthesis of N-(2-{3-(((3R)-1-(2-methylbutyl)-3-piperidyl)-  
methyl)amino-3-oxopropyl}amino-2-oxoethyl)-3,3,3- triphenyl-  
10 propanamide

To a solution of 200 mg of N-(2-{3-(((3S)-3-piperidylmethyl)-  
amino-3-oxopropyl}amino-2-oxoethyl)-3,3,3-triphenylpropanamide  
monohydrochloride in 10 ml of tetrahydrofuran, 0.10 ml of  
2-methylbutanal and 230 mg of sodium triacetoxymethylborohydrate  
15 triacetoxymethylborohydrate were successively added at room temperature,  
followed by 2 hours' stirring at the same temperature. The reaction  
liquid was diluted with ethyl acetate, washed successively with  
saturated aqueous sodium bicarbonate solution and saturated saline  
solution, and dried over anhydrous magnesium sulfate. The solvent  
20 was distilled off under reduced pressure and the resultant residue  
was purified by means of silica gel column chromatography (eluting  
solvent: chloroform/methanol = 19/1 – 4/1), to provide 158 mg of the  
title compound as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.89(3H, d, J=6.6Hz), 0.90  
25 (3H, d, J=6.6Hz), 0.95-1.20(2H, m), 1.32-1.50(1H, m),  
1.50-2.42(11H, m), 2.60-2.95(2H, m), 3.05-3.25(2H, m),  
3.34-3.50(2H, m), 3.55(2H, d, J=6.6Hz), 3.56-3.72(2H, m),  
5.75-5.98(1H, m), 6.29-6.65(2H, m), 7.10-7.38(15H, m)

FAB-MS(m/e, as (C<sub>37</sub>H<sub>48</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 597

30

## Example 2

N-(2-{3-(((3R)-1-(2-ethylbutyl)-3-piperidyl)methyl)amino-3-  
oxopropyl}amino-2-oxoethyl)-3,3,3-triphenylpropanamide]]



### 3-triphenylpropanamide

The title compound was prepared by a method similar to Step 7 of Example 1, using 2-ethylbutanal. The product was obtained in the form of a colorless solid.

5  $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.85(6\text{H}, \text{t}, J=7.4\text{Hz}), 0.94\text{-}2.46$   
(16H, m), 2.75-3.01(2H, m), 3.01-3.22(2H, m), 3.32-3.43  
(2H, m), 3.56(2H, d,  $J=5.6\text{Hz}$ ), 3.58-3.71(2H, m), 5.80-6.05  
(1H, m), 6.33-6.75(2H, m), 7.13-7.40(15H, m)  
FAB-MS(m/e, as  $(\text{C}_{38}\text{H}_{50}\text{N}_4\text{O}_3+\text{H})^+$ ): 611

10

### Example 3

N-(2-{3-(((3R)-1-(2-methylpentyl)-3-piperidyl)methyl)amino-3  
[[(- oxopropyl)amino-2-oxoethyl]-3,3,3-triphenylprepanamide]]  
- oxopropyl)amino-2-oxoethyl)-3,3,3-triphenylpropanamide

15 The title compound was prepared by a method similar to Step 7 of Example 1, using 2-methylpentanal. The product was obtained in the form of a colorless solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.80\text{-}0.98(6\text{H}, \text{m}), 0.98\text{-}1.18(2\text{H}, \text{m}),$   
1.18-1.50(4H, m), 1.51-1.99(10H, m), 2.65-3.26(4H, m),  
20 3.30-3.49(2H, m), 3.56(2H, d,  $J=5.4\text{Hz}$ ), 3.65  
(1H, d,  $J=15.8\text{Hz}$ ), 3.66(1H, d,  $J=15.8\text{Hz}$ ), 5.80-6.15(1H, m),  
6.32-6.75(2H, m), 7.12-7.40(15H, m)  
FAB-MS(m/e, as  $(\text{C}_{38}\text{H}_{50}\text{N}_4\text{O}_3+\text{H})^+$ ): 611

### 25 Example 4

N-{2-(3-(((3R)-1-propyl-3-piperidyl)methyl)amino-3-  
oxopropyl)amino-2-oxoethyl)-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to Step 7 of Example 1, using propionaldehyde. The product was  
30 obtained in the form of a colorless solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.88(3\text{H}, \text{t}, J=7.4\text{Hz}), 0.82\text{-}1.05$   
(1H, m), 1.21-2.05(8H, m), 2.20-2.45(4H, m), 2.69-2.91(2H, m),  
2.98-3.25(2H, m), 3.32-3.45(2H, m), 3.49

(1H, dd, J=5.5,16.7Hz), 3.60(1H, dd, J=5.5, 16.7Hz), 3.63  
(1H, d, J=14.9Hz), 3.65(1H, d, J=14.9Hz), 5.75-5.90(1H, m),  
5.90-6.10(1H, m), 6.20-6.32(1H, m), 7.15-7.37(15H, m)  
FAB-MS(m/e, as (C<sub>35</sub>H<sub>44</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 569

5

#### Example 5

N-{2-(3-(((3R)-1-butyl-3-piperidyl)methyl)amino-3-oxopropyl)amino-2-oxoethyl}-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to  
10 Step 7 of Example 1, using n-butylaldehyde. The product was  
obtained in the form of a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.91(3H, t, J=7.3Hz),  
0.80-2.06(10H, m), 2.10-2.64(5H, m), 2.90-3.30(4H, m),  
3.37(2H, q, J=5.9Hz), 3.45-3.65(2H, m), 3.64  
15 (1H, d, J=15.1Hz), 3.67(1H, d, J=15.1Hz), 6.31-6.49(1H, m),  
6.58-6.83(2H, m), 7.10-7.40(15H, m)  
FAB-MS(m/e, as (C<sub>36</sub>H<sub>46</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 583

#### Example 6

20 N-{2-(3-(((3R)-1-pentyl-3-piperidyl)methyl)amino-3-oxopropyl)amino-2-oxoethyl}-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to  
Step 7 of Example 1, using valeraldehyde. The product was obtained  
in the form of a colorless solid.

25 <sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.89(3H, t, J=6.9Hz),  
0.91-2.70(17H, m), 2.96-3.25(4H, m), 3.37(2H, q, J=6.0Hz),  
3.57(2H, d, J=5.4Hz), 3.65(1H, d, J=15.1Hz), 3.66  
(1H, d, J=15.1Hz), 6.53(1H, t, J=5.4Hz), 6.84(1H, t, J=5.8Hz),  
6.92(1H, t, J=5.3Hz), 7.09-7.36(15H, m)  
30 FAB-MS(m/e, as (C<sub>37</sub>H<sub>48</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 597

#### Example 7

N-{2-(3-(((3R)-1-hexyl-3-piperidyl)methyl)amino-3-

oxopropyl)amino-2-oxoethyl}-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to Step 7 of Example 1, using n-hexanal. The product was obtained in the form of a colorless solid.

- 5  $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.88(3\text{H}, \text{t}, J=6.7\text{Hz}),$   
0.91-1.82(11H, m), 1.95-2.70(8H, m), 2.95-3.20(4H, m),  
3.37(2H, q,  $J=6.0\text{Hz}$ ), 3.57(2H, d,  $J=5.7\text{Hz}$ ), 3.65  
(1H, d,  $J=15.0\text{Hz}$ ), 3.67(1H, d,  $J=15.0\text{Hz}$ ), 6.38-6.50(1H, m),  
6.67-6.88(2H, m), 7.10-7.37(15H, m)
- 10 FAB-MS(m/e, as  $(\text{C}_{38}\text{H}_{50}\text{N}_4\text{O}_3+\text{H})^+$ ): 611

Example 8

N-{2-(3-(((3R)-1-heptyl-3-piperidyl)methyl)amino-3-oxopropyl)amino-2-oxoethyl}-3,3,3-triphenylpropanamide

- 15 The title compound was prepared by a method similar to Step 7 of Example 1, using n-heptanal. The product was obtained in the form of a colorless solid.

- $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.88(3\text{H}, \text{t}, J=6.7\text{Hz}),$   
0.90-2.70(21H, m), 2.95-3.18(4H, m), 3.38(2H, q,  $J=6.1\text{Hz}$ ),  
20 3.55(1H, dd,  $J=5.6, 16.5\text{Hz}$ ), 3.59(1H, dd,  $J=5.6, 16.5\text{Hz}$ ),  
3.65(1H, d,  $J=15.1\text{Hz}$ ), 3.67(1H, d,  $J=15.1\text{Hz}$ ), 6.39  
(1H, t,  $J=5.3\text{Hz}$ ), 6.59-6.85(2H, m), 7.10-7.38(15H, m)
- FAB-MS(m/e, as  $(\text{C}_{39}\text{H}_{52}\text{N}_4\text{O}_3+\text{H})^+$ ): 625

25 Example 9

N-{2-(3-(((3R)-1-octyl-3-piperidyl)methyl)amino-3-oxopropyl)amino-2-oxoethyl}-3,3,3-triphenylpropanamide

- The title compound was prepared by a method similar to Step 7 of Example 1, using n-octanal. The product was obtained in  
30 the form of a colorless solid.

- $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.80-2.73(23\text{H}, \text{m}), 0.88$   
(3H, t,  $J=6.7\text{Hz}$ ), 2.90-3.25(4H, m), 3.29-3.48(2H, m), 3.59  
(2H, d,  $J=5.6\text{Hz}$ ), 3.65(1H, d,  $J=15.1\text{Hz}$ ), 3.68

(1H, d, J=15.1Hz), 6.25-6.42(1H, m), 6.51-6.5(2H, m),  
7.10-7.38(15H, m)

FAB-MS(m/e, as (C<sub>40</sub>H<sub>54</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 639

5 Example 10

N-{2-(3-(((3R)-1-nonyl-3-piperidyl)methyl)amino-3-oxopropyl)amino-2-oxoethyl}-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to  
Step 7 of Example 1, using n-nonanal. The product was obtained in  
10 the form of a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.88(3H, t, J=6.6Hz),  
0.80-2.73(25H, m), 2.90-3.25(4H, m), 3.28-3.50(2H, m),  
3.59(2H, d, J=5.6Hz), 3.65(1H, d, J=15.2Hz), 3.68  
(1H, d, J=15.2Hz), 6.18-6.40(1H, m), 6.48-6.85(2H, m),  
15 7.07-7.56(15H, m)

FAB-MS(m/e, as (C<sub>41</sub>H<sub>56</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 653

Example 11

N-{2-(3-(((3R)-1-decyl-3-piperidyl)methyl)amino-3-oxopropyl)amino-2-oxoethyl}-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to  
Step 7 of Example 1, using n-decanal. The product was obtained in  
the form of a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.78-2.71(30H, m), 2.88-3.25  
25 (4H, m), 3.37(2H, q, J=5.9Hz), 3.57(2H, d, J=5.6Hz), 3.65  
(1H, d, J=5.0Hz), 3.67(1H, d, J=5.0Hz), 6.49(1H, t, J=5.3Hz),  
6.75-6.95(2H, m), 7.11-7.40(15H, m)

FAB-MS(m/e, as (C<sub>42</sub>H<sub>58</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 667

30 Example 12

N-{2-(3-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)amino-3-oxopropyl)amino-2-oxoethyl}-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to

Step 7 of Example 1, using cyclohexanecarbaldehyde. The product was obtained in the form of a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.81-1.80(17H, m), 1.97-2.08  
(3H, m), 2.28-2.32(2H, m), 2.59-2.65(2H, m), 3.12-3.17(2H, m),  
5 3.37-3.46(2H, m), 3.51-3.55(2H, m), 3.64(2H, s), 5.60-5.64  
(1H, m), 6.10-6.20(1H, m), 6.26-6.30(1H, m),  
7.19-7.33(15H, m)  
FAB-MS(m/e, as (C<sub>39</sub>H<sub>50</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 623

10 Example 13

N-(2-{3-({(3R)-1-(1-cyclohepten-1-ylmethyl)-3-piperidyl}-methyl)amino-3-oxopropyl}amino-2-oxoethyl)-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to  
15 Step 7 of Example 1, using 1-cycloheptenecarbaldehyde (cf. WO 9633973). The product was obtained in the form of a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.95-2.40(21H, m), 2.70-3.25  
(4H, m), 3.40(2H, q, J=5.9Hz), 3.56(2H, d, J=5.6Hz), 3.64  
(1H, d, J=15.7Hz), 3.66(1H, d, J=15.7Hz), 5.71-6.81(4H, m),  
20 7.09-7.40(15H, m)  
FAB-MS(m/e, as (C<sub>40</sub>H<sub>50</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 635

Example 14

N-(2-{3-({(3R)-1-(1-cyclononen-1-ylmethyl)-3-piperidyl}-methyl)amino-3-oxopropyl}amino-2-oxoethyl)-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to  
Step 7 of Example 1, using 1-cyclononenecarbaldehyde (cf. WO 9804554). The product was obtained in the form of a colorless solid.

30 <sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.78-2.41(25H, m), 2.51-3.47  
(6H, m), 3.56(2H, d, J=5.4Hz), 3.65(1H, d, J=15.9Hz),  
3.66(1H, d, J=15.9Hz), 5.38-6.83(4H, m), 7.05-7.38(15H, m)  
FAB-MS(m/e, as (C<sub>42</sub>H<sub>54</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 663

Example 15

N-{2-(3-(((3S)-1-heptyl-3-piperidyl)methyl)amino-3-oxopropyl)amino-2-oxoethyl}-3,3,3-triphenylpropanamide

5           The title compound was prepared by successively conducting procedures similar to Steps 5 and 6 of Example 1 and Example 8, using (3S)-3-aminomethyl-1-(tert-butoxycarbonyl)piperidine. The product was obtained as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.88(3H, t, J=6.8Hz), 0.80-2.02  
10           (17H, m), 2.20-2.41(4H, m), 2.70-2.90(2H, m), 2.90-3.20 (2H, m), 3.35-3.45(2H, m), 3.47(1H, dd, J=5.5, 16.6Hz), 3.57(1H, dd, J=5.5, 16.6Hz), 3.62(1H, d, J=15.0Hz), 3.65 (1H, d, J=15.0Hz), 6.09(1H, t, J=5.3Hz), 6.18-6.35(1H, m), 6.48(1H, t, J=5.6Hz), 7.10-7.39(15H, m)

15           FAB-MS(m/e, as (C<sub>39</sub>H<sub>52</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 625

Example 16

N-{2-(3-(((3S)-1-cyclohexylmethyl-3-piperidyl)methyl)amino-3-oxopropyl)amino-2-oxoethyl}-3,3,3-triphenylpropanamide

20           The title compound was prepared by successively conducting procedures similar to Steps 5 and 6 of Example 1 and Example 12, using (3S)-3-aminomethyl-1-(tert-butoxycarbonyl)piperidine. The product was obtained as a pale yellow solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.81-1.80(17H, m), 1.97-2.08  
25           (3H, m), 2.28-2.32(2H, m), 2.59-2.65(2H, m), 3.12-3.17(2H, m), 3.37-3.46(2H, m), 3.51-3.55(2H, m), 3.64(2H, s), 5.60-5.64 (1H, m), 6.10(1H, brs), 6.26-6.30(1H, m), 7.19-7.33(15H, m)

FAB-MS(m/e, as (C<sub>39</sub>H<sub>50</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 623

30   Example 17

N-{(1S)-2-(3-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-amino-3-oxopropyl)amino-1-(2-carbamoylethyl)-2-oxoethyl}-3,3,3-triphenylpropanamide

(Step 1)

Synthesis of 3-(benzyloxycarbonyl)amino-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)propanamide

The title compound was prepared by a method similar to  
5    Step 5 of Example 1, using N-benzyloxycarbonyl-L-alanine.

(Step 2)

Synthesis of 3-(benzyloxycarbonyl)amino-N-(((3S)-3-piperidyl)methyl)propanamide

To a solution of 1.84 g of 3-(benzyloxycarbonyl)amino-N-  
10    (((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)propanamide in 2  
ml of chloroform, 2 ml of trifluoroacetic acid was added at room  
temperature, followed by an hour's stirring at the same temperature.  
The reaction liquid was distilled off under reduced pressure, and the  
residue was rendered basic with 4N aqueous sodium hydroxide  
15    solution. Extracting the product with chloroform, the product was  
dried over anhydrous sodium sulfate. Upon distilling the solvent off  
under reduced pressure, 1.26 g of the title compound was obtained.

(Step 3)

Synthesis of 3-(benzyloxycarbonyl)amino-N-(((3R)-1-  
20    cyclohexylmethyl-3-piperidyl)methyl)propanamide

To a solution of 600 mg of 3-(benzyloxycarbonyl)amino-N-  
(((3S)-3-piperidyl)methyl)propanamide in 3 ml of methanol, a solution  
of 150 mg of sodium ~~cyanoborohydrate~~ cyanoborohydride and 160 mg  
of zinc chloride in 8.1 ml of methanol, and 0.30 ml of  
25    cyclohexanecarbaldehyde were added at room temperature, followed  
by an hour's stirring at the same temperature. The reaction liquid  
was diluted with ethyl acetate and successively washed with  
saturated aqueous sodium bicarbonate solution and saturated saline,  
followed by drying over anhydrous sodium sulfate. Upon distilling  
30    the solvent off under reduced pressure, 775 mg of the title compound  
was obtained.

(Step 4)

Synthesis of 3-amino-N-(((3R)-1-cyclohexylmethyl-3-

piperidyl)methyl}propanamide

To a solution of 770 mg of 3-(benzyloxycarbonyl)amino-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl}propanamide in 12 ml of methanol, 0.5 ml of 10% hydrochloric acid-methanol and 15 mg  
5 of 20% palladium hydroxide-carbon catalyst were added, followed by 44 hours' stirring under 3 atmospheres of hydrogen. Filtering the catalyst off, the solvent was distilled off under reduced pressure, and the residue was rendered weakly basic with saturated aqueous sodium bicarbonate solution. The product was extracted with  
10 chloroform and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified by means of silica gel column chromatography (eluting solvent: chloroform-chloroform/methanol/28% aqueous ammonia = 100/10/1) to provide 391 mg of the title compound.

15 (Step 5)

Synthesis of (2S)-2-amino-N<sup>5</sup>-triphenylmethyl-N<sup>1</sup>-(3-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl}amino-3-oxopropyl)-pentanediamide monohydrochloride

The title compound was prepared by procedures similar to  
20 Steps 5-6 of Example 1, using 3-amino-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl}propanamide and N- $\alpha$ -(tert-butoxycarbonyl)- $\gamma$ -triphenylmethyl-L-glutamine.

(Step 6)

Synthesis of N-((1S)-2-(3-(((3R)-1-cyclohexylmethyl-3-  
25 piperidyl)methyl}amino-3-oxopropyl)amino-1-(2-carbamoylethyl)-2-oxoethyl)-3,3,3-triphenylpropanamide

To a solution of 84 mg of (2S)-2-amino-N<sup>5</sup>-triphenylmethyl-N<sup>1</sup>-(3-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl}amino-3-oxopropyl)pentanediamide monohydrochloride in 1.5 ml of chloroform,  
30 0.052 ml of N,N-diisopropylethylamine was added at room temperature, followed by an hour's stirring at the same temperature. Then 39 mg of 3,3,3-triphenylpropionic acid, 24 mg of 1-hydroxybenzotriazole monohydrate and 31 mg of 1-ethyl-3-(3-dimethyl-



aminopropyl)carbodiimide monohydrochloride were added at room temperature by the order stated, followed by 17 hours' stirring at the same temperature. The reaction liquid was rendered weakly basic with saturated aqueous sodium bicarbonate solution, extracted with chloroform and dried over anhydrous sodium sulfate. Distilling the solvent off under reduced pressure, the resultant residue was dissolved in 1 ml of chloroform, and to the solution 1 ml of trifluoroacetic acid was added at room temperature, followed by 20 minutes' stirring at the same temperature. The reaction liquid was rendered weakly basic with saturated aqueous sodium bicarbonate solution, extracted with chloroform and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified with preparative thin layer chromatography (Kieselgel™60F<sub>254</sub>, Art 5744 (Merck), chloroform/methanol/28% aqueous ammonia = 90/10/1) to provide 43 mg of the title compound as a white solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD, δppm): 0.80-2.00(22H, m), 2.06-2.18 (2H, m), 2.23-2.33(2H, m), 2.73-2.87(2H, m), 2.90-3.08 (2H, m), 3.20-3.38(2H, m), 3.58(1H, d, J=15.0Hz), 3.86 (1H, d, J=15.0Hz), 3.84-3.91(1H, m), 7.10-7.28(15H, m)  
FAB-MS(m/e, as (C<sub>42</sub>H<sub>55</sub>N<sub>5</sub>O<sub>4</sub>+H)<sup>+</sup>): 694

#### Example 18

N-{(1R)-2-(3-{(1-cyclohexylmethyl-3-piperidyl)methyl}amino-3-oxopropyl)amino-1-(2-carbamoyl-ethyl)-2-oxoethyl}-3,3,3-triphenylpropanamide

(Step 1)

Synthesis of 3-amino-N-{(1-cyclohexylmethyl-3-piperidyl)methyl}propanamide

The title compound was prepared by procedures similar to Steps 1-4 of Example 17, using 3-aminomethyl-1-(tert-butoxy-carbonyl)piperidine.

(Step 2)

Synthesis of N-((1R)-2-(3-((1-cyclohexylmethyl-3-piperidyl)methyl)amino-3-oxopropyl)amino-1-(2-carbamoylethyl)-2-oxoethyl)-3,3,3-triphenylpropanamide

The title compound was prepared by procedures similar to  
5 Steps 5-6 of Example 17 using 3-amino-N-((1-cyclohexylmethyl-3-piperidyl)methyl)propanamide and N- $\alpha$ -(tert-butoxycarbonyl)- $\gamma$ -triphenylmethyl-D-glutamine. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD,  $\delta$ ppm): 0.80-0.98(3H, m), 1.15-1.32  
10 (3H, m), 1.47-2.00(16H, m), 2.13(2H, d, J=6.9Hz), 2.31  
(2H, t, J=6.4Hz), 2.86-2.87(2H, m), 2.98-3.04(2H, m),  
3.30-3.37(2H, m), 3.58(1H, d, J=15.0Hz), 3.86  
(1H, d, J=15.0Hz), 3.87-3.91(1H, m), 7.13-7.30(15H, m)

FAB-MS(m/e, as (C<sub>42</sub>H<sub>55</sub>N<sub>5</sub>O<sub>4</sub>+H)<sup>+</sup>): 694

Example 19

N-((1S)-2-(3-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-  
5 amino-3-oxopropyl)amino-1-(1H-imidazol-4-ylmethyl)-2-oxoethyl)-  
3,3,3-triphenylpropanamide

The title compound was prepared by successively conducting  
procedures similar to Step 5 of Example 17 and Step 3 of Example 1,  
using (tert-butoxycarbonyl)-N-imidazole-benzyloxycarbonyl-L-  
10 histidine. The compound was obtained as a white foamy substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.73-2.00(20H, m), 2.02-2.28  
(4H, m), 2.55-2.64(1H, m), 2.67-2.98(3H, m), 3.15-3.33  
(2H, m), 3.60-3.77(2H, m), 4.25-4.34(1H, m), 6.18-6.40  
(2H, m), 6.69(1H, s), 7.15-7.50(16H, m), 7.44(1H, s)

15 FAB-MS(m/e, as (C<sub>43</sub>H<sub>54</sub>N<sub>6</sub>O<sub>3</sub>+H)<sup>+</sup>): 703

Example 20

N-((1R)-2-(3-((1-cyclohexylmethyl-3-piperidyl)methyl)amino-  
3-oxopropyl)amino-1-(1H-imidazol-4-ylmethyl)-2-oxoethyl)-3,3,3-tri-  
20 phenylpropanamide

The title compound was prepared by a method similar to  
Example 19, using 3-amino-N-((1-cyclohexylmethyl-3-piperidyl)-  
methyl}propanamide and N-α, imidazole-di-(tert-butoxycarbonyl)-D-  
histidine. The compound was obtained as a white solid.

25 <sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.75-1.80(19H, m), 1.80-1.98  
(1H, m), 2.03-2.22(4H, m), 2.56-2.64(1H, m), 2.66-2.92(3H, m),  
3.13-3.32(2H, m), 3.62-3.75(2H, m), 4.25-4.34(1H, m),  
6.36-6.52(1H, m), 6.57(1H, s), 6.55-6.70(1H, m), 7.14-7.32  
(16H, m), 7.41(1H, s)

30 FAB-MS(m/e, as (C<sub>43</sub>H<sub>54</sub>N<sub>6</sub>O<sub>3</sub>+H)<sup>+</sup>): 703

Example 21

N-((1S)-2-(3-((1-cyclohexylmethyl-3-piperidyl)methyl)amino-

3-oxopropyl)amino-1-(2-hydroxyethyl)-2-oxoethyl}-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to Example 19, using 3-amino-N-((1-cyclohexylmethyl-3-piperidyl)-methyl}propanamide and N-(tert-butoxycarbonyl)-L-homoserine. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.75-0.90(2H, m), 0.92-1.07(1H,m), 1.10-1.98(17H, m), 2.03-2.10(2H, m), 2.25-2.34(2H, m), 2.60-2.70(2H, m), 3.02-3.21(3H, m), 3.33-3.44(3H, m), 3.51-3.58(1H, m), 3.67-3.79(2H, m), 4.18-4.27(1H, m), 6.16-6.22(1H, m), 6.22-6.34(1H, m), 6.67-6.75(1H, m), 7.15-7.32(15H, m)

FAB-MS(m/e, as (C<sub>41</sub>H<sub>54</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 667

Example 22

N-{2-(3-(((3R)-1-heptyl-3-piperidyl)methyl}amino-3-oxopropyl)-amino-2-oxoethyl}-N-methyl-3,3,3-triphenylpropanamide

The title compound was prepared by successively conducting procedures similar to Steps 1-6 of Example 1 and Example 8, using N-(tert-butoxycarbonyl)-N-methyl-glycine. The compound was obtained as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.79-2.00(20H, m), 2.17-3.81 (17H, m), 5.80-6.75(2H, m), 7.10-7.35(15H, m)

FAB-MS(m/e, as (C<sub>40</sub>H<sub>54</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 639

25

Example 23

N-{2-(3-((1-heptyl-3-piperidyl)methyl}amino-3-oxopropyl)-amino-2-oxoethyl}-N-methyl-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to Example 22, using 3-aminomethyl-1-(tert-butoxycarbonyl)piperidine. The compound was obtained as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.79-2.00(20H, m), 2.17-3.81 (17H, m), 5.80-6.75(2H, m), 7.10-7.35(15H, m)

FAB-MS(m/e, as (C<sub>40</sub>H<sub>54</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 639

Example 24

N-{6-(((3S)-3-piperidyl)methyl)amino-6-oxohexyl}-3,3,3-  
5 triphenylpropanamide  
(Step 1)

Synthesis of methyl 6-((tert-butoxycarbonyl)amino)-  
hexanoate

1.28 Grams of 6-((tert-butoxycarbonyl)amino)hexanoic acid  
10 was dissolved in a liquid mixture of 9 ml of chloroform and 3 ml of  
methanol. To the solution 1.27 g of 1-ethyl-3-(3-dimethylamino-  
propyl)carbodiimide monohydrochloride and 7 mg of 4-dimethyl-  
aminopyridine were successively added at room temperature, followed  
by 2 hours' stirring at the same temperature. The reaction liquid  
15 was diluted with chloroform, washed successively with saturated  
aqueous sodium bicarbonate solution and saturated aqueous  
ammonium chloride solution, and dried over anhydrous sodium  
sulfate. Distilling the solvent off under reduced pressure, 1.03 g of  
the title compound was obtained.

20 (Step 2)

Synthesis of N-{6-(((3S)-3-piperidyl)methyl)amino-6-  
oxohexyl}-3,3,3- triphenylpropanamide

The title compound was prepared by successively conducting  
procedures similar to Steps 2-5 of Example 1 and Step 2 of Example  
25 17, using methyl 6-((tert-butoxycarbonyl)amino)hexanoate. The  
compound was obtained as a white foamy substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.98-1.82(12H, m), 2.06  
(2H, t, J=7.5Hz), 2.31(1H, t, J=11.0Hz), 2.52-2.62(1H, m),  
2.87-3.06(4H, m), 3.10(2H, q, J=6.6Hz), 3.55(2H, s),  
30 4.87-4.96(1H, m), 5.65-5.72(1H, m), 7.15-7.38(15H, m)

FAB-MS(m/e, as (C<sub>33</sub>H<sub>41</sub>N<sub>3</sub>O<sub>2</sub>+H)<sup>+</sup>): 512

Example 25

N-{6-(((3R)-1-(2-methylbutyl)-3-piperidyl)methyl)amino-6-oxohexyl}-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to Step 3 of Example 17, using N-{6-(((3S)-3-piperidyl)methyl)amino-6-oxohexyl}-3,3,3-triphenylpropanamide and 2-methylbutanal. The compound was obtained as a white foamy substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.84-0.91(6H, m), 0.95-1.16 (6H, m), 1.36-2.19(14H, m), 2.59-2.72(2H, m), 2.87-2.95 (2H, m), 3.09-3.27(2H, m), 3.56(2H,s), 4.82-4.90(1H, m), 5.80-5.92(1H, m), 7.18-7.32(15H, m)

FAB-MS(m/e, as (C<sub>38</sub>H<sub>51</sub>N<sub>3</sub>O<sub>2</sub>+H)<sup>+</sup>): 582

Example 26

N-{6-(((3R)-1-(2-methylpentyl)-3-piperidyl)methyl)amino-6-oxohexyl}-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to Example 25, using 2-methylpentanal. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.85-0.95(6H, m), 0.97-1.16 (6H, m), 1.18-2.22(16H, m), 2.62-2.78(2H, m), 2.87-2.94 (2H, m), 3.08-3.25(2H, m), 3.56(2H, s), 4.80-4.88(1H, m), 5.80-5.92(1H, m), 7.18-7.37(15H, m)

FAB-MS(m/e, as (C<sub>39</sub>H<sub>53</sub>N<sub>3</sub>O<sub>2</sub>+H)<sup>+</sup>): 596

Example 27

N-(6-(((3R)-1-ethyl-3-piperidyl)methyl)amino-6-oxohexyl)-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to Example 25, using acetaldehyde. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.90-1.03(2H, m), 1.07 (6H, t, J=7.1Hz), 1.43-1.80(7H, m), 1.85-2.96(1H, m), 2.07 (2H, t, J=7.6Hz), 2.38(2H, q, J=7.2Hz), 2.78-2.85(2H, m),

2.85-2.96(2H, m), 3.10-3.20(2H, m), 3.56(2H, s), 2.78-4.88  
(1H, m), 5.77-5.67(1H, m), 7.17-7.38(15H, m)  
FAB-MS(m/e, as (C<sub>35</sub>H<sub>45</sub>N<sub>3</sub>O<sub>2</sub>+H)<sup>+</sup>): 540

5 Example 28

N-(6-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)amino-6-oxohexyl)-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to  
Example 25, using cyclohexanecarbaldehyde. The compound was  
10 obtained as a white foamy substance

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.80-1.80(23H, m), 1.95-2.08  
(5H, m), 2.57-2.65(2H, m), 2.87-2.94(2H, m), 3.13-3.20(2H, m),  
3.56(2H, s), 4.78-4.81(1H, m), 5.78-5.80(1H, m),  
7.20-7.32(15H, m)

15 FAB-MS(m/e, as (C<sub>40</sub>H<sub>53</sub>N<sub>3</sub>O<sub>2</sub>+H)<sup>+</sup>): 608

Example 29

N-{6-(3-piperidylmethyl)amino-6-oxohexyl}-3,3,3-triphenylpropanamide

20 The title compound was prepared by a method similar to  
Example 24, using 3-aminomethyl-1-(tert-butoxycarbonyl)piperidine.  
The compound was obtained as a white foamy substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.98-1.82(12H, m), 2.06  
(2H, t, J=7.5Hz), 2.31(1H, t, J=11.0Hz), 2.52-2.62(1H, m),  
25 2.87-3.06(4H, m), 3.10(2H, q, J=6.6Hz), 3.55(2H, s),  
4.87-4.96(1H, m), 5.65-5.72(1H, m), 7.15-7.38(15H, m)

FAB-MS(m/e, as (C<sub>33</sub>H<sub>41</sub>N<sub>3</sub>O<sub>2</sub>+H)<sup>+</sup>): 512

Example 30

30 N-(6-((1-butyl-3-piperidyl)methyl)amino-6-oxohexyl)-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to  
Step 3 of Example 17, using N-{6-(3-piperidylmethyl)amino-6-

oxohexyl}-3,3,3-triphenylpropanamide and n-butylaldehyde. The compound was obtained as a white solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.88\text{-}1.13(8\text{H}, \text{m}), 1.24\text{-}1.40$   
 $(2\text{H}, \text{m}), 1.43\text{-}1.78(7\text{H}, \text{m}), 1.83\text{-}1.98(2\text{H}, \text{m}), 2.04\text{-}2.16(3\text{H}, \text{m}),$   
5  $2.38\text{-}2.48(2\text{H}, \text{m}), 2.85\text{-}2.97(4\text{H}, \text{m}), 3.08\text{-}3.23(2\text{H}, \text{m}),$   
 $3.56(2\text{H}, \text{s}), 4.83\text{-}4.92(1\text{H}, \text{m}), 5.78\text{-}5.88(1\text{H}, \text{m}),$   
 $7.15\text{-}7.32(15\text{H}, \text{m})$

FAB-MS(m/e, as  $(\text{C}_{37}\text{H}_{49}\text{N}_3\text{O}_2+\text{H})^+$ ): 568

#### 10 Example 31

N-(6-((1-isobutyl-3-piperidyl)methyl)amino-6-oxohexyl)-  
3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to  
Example 30, using isobutylaldehyde. The compound was obtained as  
15 a colorless oily substance.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.80\text{-}2.33(24\text{H}, \text{m}), 2.60\text{-}3.05$   
 $(4\text{H}, \text{m}), 3.05\text{-}3.33(2\text{H}, \text{m}), 3.56(2\text{H}, \text{s}), 4.77\text{-}5.02(1\text{H}, \text{m}),$   
 $5.80\text{-}6.10(1\text{H}, \text{m}), 7.10\text{-}7.55(15\text{H}, \text{m})$

FAB-MS(m/e, as  $(\text{C}_{37}\text{H}_{49}\text{N}_3\text{O}_2+\text{H})^+$ ): 568

20

#### Example 32

N-(6-((1-(2-ethylbutyl)-3-piperidyl)methyl)amino-6-oxohexyl)-  
3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to  
25 Example 30, using 2-ethylbutanal. The compound was obtained as a  
white solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.85(6\text{H}, \text{t}, \text{J}=7.4\text{Hz}), 0.93\text{-}1.19$   
 $(5\text{H}, \text{m}), 1.19\text{-}1.78(10\text{H}, \text{m}), 1.78\text{-}2.30(7\text{H}, \text{m}), 2.60\text{-}3.00$   
 $(4\text{H}, \text{m}), 3.03\text{-}3.31(2\text{H}, \text{m}), 3.56(2\text{H}, \text{s}), 4.77\text{-}4.96(1\text{H}, \text{m}),$   
30  $5.82\text{-}6.03(1\text{H}, \text{m}), 7.10\text{-}7.38(15\text{H}, \text{m})$

FAB-MS(m/e, as  $(\text{C}_{39}\text{H}_{53}\text{N}_3\text{O}_2+\text{H})^+$ ): 596

#### Example 33



N-(6-((1-cyclohexyl-3-piperidyl)methyl)amino-6-oxohexyl)-  
3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to  
Example 30, using cyclohexanone. The compound was obtained as a  
5 white solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.83\text{-}1.38(10\text{H}, \text{m}), 1.40\text{-}1.94$   
 $(11\text{H}, \text{m}), 2.00\text{-}2.17(3\text{H}, \text{m}), 2.20\text{-}2.48(2\text{H}, \text{m}), 2.50\text{-}3.03$   
 $(4\text{H}, \text{m}), 3.03\text{-}3.28(2\text{H}, \text{m}), 3.56(2\text{H}, \text{s}), 4.79\text{-}4.97(1\text{H}, \text{m}),$   
 $5.82\text{-}6.03(1\text{H}, \text{m}), 7.15\text{-}7.40(15\text{H}, \text{m})$

10 FAB-MS(m/e, as  $(\text{C}_{39}\text{H}_{51}\text{N}_3\text{O}_2+\text{H})^+$ ): 594

Example 34

N-(6-((1-benzyl-3-piperidyl)methyl)amino-6-oxohexyl)-  
3,3,3-triphenylpropanamide

15 The title compound was prepared by a method similar to  
Example 30, using benzaldehyde. The compound was obtained as a  
colorless oily substance.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.80\text{-}1.88(11\text{H}, \text{m}), 1.90\text{-}2.45$   
 $(4\text{H}, \text{m}), 2.75\text{-}3.28(6\text{H}, \text{m}), 3.55(2\text{H}, \text{s}), 3.65\text{-}3.92(2\text{H}, \text{m}),$   
20  $4.78\text{-}5.00(1\text{H}, \text{m}), 6.05\text{-}6.30(1\text{H}, \text{m}), 7.06\text{-}7.60(20\text{H}, \text{m})$

FAB-MS(m/e, as  $(\text{C}_{40}\text{H}_{47}\text{N}_3\text{O}_2+\text{H})^+$ ): 602

Example 35

N-(6-((1-cyclooctylmethyl-3-piperidyl)methyl)amino-6-  
25 oxohexyl)-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to  
Example 30, using cyclooctanecarbaldehyde. The compound was  
obtained as a white solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.98\text{-}2.10(32\text{H}, \text{m}), 2.60\text{-}2.70$   
30  $(2\text{H}, \text{m}), 2.87\text{-}2.93(2\text{H}, \text{m}), 3.08\text{-}3.28(2\text{H}, \text{m}), 3.56(2\text{H}, \text{m}),$   
 $4.79\text{-}4.87(1\text{H}, \text{m}), 5.82\text{-}5.92(1\text{H}, \text{m}), 7.18\text{-}7.30(15\text{H}, \text{m})$

FAB-MS(m/e, as  $(\text{C}_{42}\text{H}_{57}\text{N}_3\text{O}_2+\text{H})^+$ ): 636

Example 36

N-{6-((1-(1-cyclononen-1-ylmethyl)-3-piperidyl)methyl)-amino-6-oxohexyl}-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to Example 30, using 1-cyclononenecarbaldehyde (WO9804554). The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.95-1.80(22H, m), 1.90-1.98 (7H,m), 2.58-2.70(2H, m), 2.77(2H, s), 2.87-2.93(2H, m), 3.12-3.18(2H, m), 3.56(2H, s), 4.78-4.85(1H, m), 5.36-5.43 (1H,m), 5.65-5.75(1H, m), 7.18-7.30(15H, m)  
FAB-MS(m/e, as (C<sub>43</sub>H<sub>57</sub>N<sub>3</sub>O<sub>2</sub>+H)<sup>+</sup>): 648

Example 37

N-(6-((1-allyl-3-piperidyl)methyl)amino-6-oxohexyl)-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to Example 30, using acrylaldehyde. The compound was obtained as a pale yellow solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.78-2.24(15H, m), 2.68-3.27 (8H,m), 3.56(2H, s), 4.70-4.93(1H, m), 5.05-5.28(2H, m), 5.50-5.72(1H,m), 5.75-5.98(1H, m), 7.10-7.50(15H, m)  
FAB-MS(m/e, as (C<sub>36</sub>H<sub>45</sub>N<sub>3</sub>O<sub>2</sub>+H)<sup>+</sup>): 552

Example 38

N-{6-(((3S)-1-(2-methylbutyl)-3-piperidyl)methyl)amino-6-oxohexyl}-3,3,3-triphenylpropanamide

The title compound was prepared by successively conducting methods which are similar to Examples 24 and 25, using (3S)-3-aminomethyl-1-(tert-butoxycarbonyl)piperidine. The compound was obtained as a white foamy substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.83-0.92(6H, m), 0.97-1.16 (6H, m), 1.36-1.95(9H, m), 2.02-2.21(5H, m), 2.60-2.73(2H, m), 2.87-2.95 (2H, m), 3.08-3.27(2H, m), 3.56(2H, s), 4.79-4.88

(1H, m), 5.78-5.90(1H, m), 7.17-7.33(15H, m)

FAB-MS(m/e, as (C<sub>38</sub>H<sub>51</sub>N<sub>3</sub>O<sub>2</sub>+H)<sup>+</sup>): 582

### Example 39

5        (2R)-N-(((3S)-3-piperidylmethyl)-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide  
(Step 1)

Synthesis of methyl (2R)-pyrrolidine-2-carboxylate monohydrochloride

10        The title compound was prepared by successively conducting methods which are similar to Step 1 of Example 24 and Step 2 of Example 1, using N-(tert-butoxycarbonyl)-D-proline.  
(Step 2)

15        Synthesis of (2R)-N-(((3S)-3-piperidylmethyl)-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

The title compound was prepared by successively conducting methods which are similar to Steps 1-5 of Example 1 and Step 2 of Example 17, using methyl (2R)-pyrrolidine-2-carboxylate monohydrochloride and N-(tert-butoxycarbonyl)-L-proline. The compound was obtained as a colorless oily substance.

25        <sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.93-1.52(3H, m), 1.55-2.03 (10H,m), 2.11(1H, t, J=10.1Hz), 2.25-2.33(1H, m), 2.48-2.57 (1H,m), 2.66-2.80(2H, m), 2.88-3.02(3H, m), 3.28-3.42(2H, m), 3.43(1H, d, J=14.6Hz), 3.78-3.86(1H, m), 3.91 (1H, d, J=14.6Hz), 4.10 (1H, t, J=7.1Hz), 4.57(1H, d, J=8.2Hz), 7.15-7.30(16H,m)

FAB-MS(m/e, as (C<sub>37</sub>H<sub>44</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 593

### 30        Example 40

(2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Step 3 of Example 17, using (2R)-N-((3S)-3-piperidylmethyl)-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide. The compound was obtained as a white foamy substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.78-0.91(4H, m), 1.10-1.30(5H, m), 1.32-1.97(16H, m), 2.00-2.09(2H, m), 2.25-2.33(1H, m), 2.50-2.83(4H, m), 3.04-3.13(1H, m), 3.27-3.38(2H, m), 3.41(1H, d, J=14.6Hz), 3.77-3.86(1H, m), 3.90(1H, d, J=14.6Hz), 4.06-4.12(1H, m), 4.55-4.62(1H, m), 7.13-7.32(16H, m)

FAB-MS(m/e, as (C<sub>44</sub>H<sub>56</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 689

#### Example 41

(2R)-N-(3-piperidylmethyl)-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide monohydrochloride  
(Step 1)

Synthesis of (2R)-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxylic acid

The title compound was prepared by conducting procedures similar to Steps 1-4 of Example 1, using methyl (2R)-pyrrolidine-2-carboxylate monohydrochloride and N-(tert-butoxycarbonyl)-L-proline.

(Step 2)

Synthesis of (2R)-N-(3-piperidylmethyl)-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide monohydrochloride

The title compound was prepared by conducting procedures similar to Steps 5-6 of Example 1, using (2R)-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxylic acid and 3-aminomethyl-1-(tert-butoxycarbonyl)piperidine. The compound was obtained as a white solid.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta\text{ppm}): 1.10\text{-}2.16(15\text{H}, \text{m}), 2.34\text{-}2.53$   
 $(1\text{H}, \text{m}), 2.60\text{-}3.16(5\text{H}, \text{m}), 3.34\text{-}3.54(3\text{H}, \text{m}), 3.70\text{-}3.90(2\text{H}, \text{m}),$   
 $4.12\text{-}4.19(1\text{H}, \text{m}), 4.35\text{-}4.40(1\text{H}, \text{m}), 7.10\text{-}7.30(15\text{H}, \text{m})$   
 $\text{FAB-MS}(\text{m/e}, \text{as } (\text{C}_{37}\text{H}_{44}\text{N}_4\text{O}_3+\text{H})^+): 593$

5

#### Example 42

(2R)-N-((1-methyl-3-piperidyl)methyl)-1-((2S)-1-(3,3,3-  
triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-  
carboxamide

10        The title compound was prepared by a method similar to  
Step 7 of Example 1 using (2R)-N-(3-piperidylmethyl)-1-((2S)-1-  
(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-  
carboxamide monohydrochloride and 37% ~~aqueous~~ aqueous  
formaldehyde solution. The compound was obtained as a white solid.

15         $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.85\text{-}2.05(13\text{H}, \text{m}), 2.23\text{-}2.35$   
 $(4\text{H}, \text{m}), 2.46\text{-}2.58(1\text{H}, \text{m}), 2.65\text{-}3.90(3\text{H}, \text{m}), 2.99\text{-}3.17$   
 $(1\text{H}, \text{m}), 3.28\text{-}3.47(3\text{H}, \text{m}), 3.78\text{-}3.90(2\text{H}, \text{m}), 3.99\text{-}4.15$   
 $(2\text{H}, \text{m}), 4.53\text{-}4.62(1\text{H}, \text{m}), 7.13\text{-}7.38(16\text{H}, \text{m})$   
 $\text{FAB-MS}(\text{m/e}, \text{as } (\text{C}_{38}\text{H}_{46}\text{N}_4\text{O}_3+\text{H})^+): 607$

20

#### Example 43

(2R)-N-((1-benzyl-3-piperidyl)methyl)-1-((2S)-1-(3,3,3-  
triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-  
carboxamide

25        The title compound was prepared by a method similar to  
Example 42, using benzaldehyde. The compound was obtained as a  
white solid.

30         $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.75\text{-}2.00(14\text{H}, \text{m}), 2.11\text{-}2.28$   
 $(1\text{H}, \text{m}), 2.37\text{-}2.58(1\text{H}, \text{m}), 2.60\text{-}2.70(1\text{H}, \text{m}), 2.74\text{-}2.90$   
 $(2\text{H}, \text{m}), 3.02\text{-}3.29(2\text{H}, \text{m}), 3.32\text{-}3.56(4\text{H}, \text{m}), 3.56\text{-}3.67$   
 $(1\text{H}, \text{m}), 3.82\text{-}3.97(1\text{H}, \text{m}), 4.00\text{-}4.13(1\text{H}, \text{m}), 4.52\text{-}4.60$   
 $(1\text{H}, \text{m}), 7.10\text{-}7.40(21\text{H}, \text{m})$   
 $\text{FAB-MS}(\text{m/e}, \text{as } (\text{C}_{44}\text{H}_{50}\text{N}_4\text{O}_3+\text{H})^+): 683$

Example 44

(2R)-N-((1-cyclohexylmethyl-3-piperidyl)methyl)-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Example 42, using cyclohexanecarbaldehyde. The compound was obtained as a white solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.75\text{-}0.92(4\text{H}, \text{m}), 1.11\text{-}1.22(4\text{H}, \text{m}), 1.23\text{-}2.10(19\text{H}, \text{m}), 2.24\text{-}2.33(1\text{H}, \text{m}), 2.50\text{-}2.86(4\text{H}, \text{m}), 2.98\text{-}3.14(1\text{H}, \text{m}), 3.26\text{-}3.38(2\text{H}, \text{m}), 3.41(1\text{H}, \text{d}, J=14.5\text{Hz}), 3.77\text{-}3.85(1\text{H}, \text{m}), 3.87(1\text{H}, \text{d}, J=14.5\text{Hz}), 4.06\text{-}4.16(1\text{H}, \text{m}), 4.57\text{-}4.61(1\text{H}, \text{m}), 7.14\text{-}7.35(16\text{H}, \text{m})$   
FAB-MS(m/e, as  $(\text{C}_{44}\text{H}_{56}\text{N}_4\text{O}_3+\text{H})^+$ ): 689

Example 45

(2R)-1-((2S, 4R)-4-tert-butoxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-N-((3S)-3-piperidylmethyl)pyrrolidine-2-carboxamide

(Step 1)

Synthesis of (2R)-1-benzyloxycarbonyl-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Step 5 of Example 1, using N-benzyloxycarbonyl-D-proline.

(Step 2)

Synthesis of (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)-pyrrolidine-2-carboxamide

To a solution of 2.49 g of (2R)-1-benzyloxycarbonyl-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)pyrrolidine-2-carboxamide in 20 ml of methanol, 15 mg of 20% palladium hydroxide-carbon catalyst was added, followed by 5 hours' stirring in hydrogen atmosphere. After filtering the catalyst off, the solvent was distilled off under reduced pressure to provide 1.78 g of the title

compound.

(Step 3)

Synthesis of (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)-1-((2S, 4R)-4-(tert-butoxy)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

The title compound was prepared by methods similar to Steps 1 and 2 of Example 45, using (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)pyrrolidine-2-carboxamide and N-benzyloxycarbonyl-O-(tert-butyl)-trans-4-hydroxy-L-proline.

(Step 4)

Synthesis of (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)-1-((2S, 4R)-4-(tert-butoxy)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

To a solution of 2.12 g of (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)-1-((2S, 4R)-4-(tert-butoxy)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide and 1.67 g of 3,3,3-triphenylpropionic acid in 25 ml of chloroform, 944 mg of 1-hydroxybenzotriazole monohydrate and 1.18 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide monohydrochloride were successively added at room temperature, followed by 40 hours' stirring at the same temperature. The reaction liquid was diluted with chloroform, washed with saturated aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by means of silica gel column chromatography (eluting solvent: from hexane/ethyl acetate = 2/1 to ethyl acetate) to provide 2.98 g of the title compound.

(Step 5)

Synthesis of (2R)-1-((2S, 4R)-4-tert-butoxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-N-((3S)-3-piperidylmethyl)pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Step 2 of Example 17, using (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-

piperidyl)methyl)-1-((2S, 4R)-4-(tert-butoxy)-1-(3,3,3-triphenyl-  
[[propanoyl]pyrrolidin-2-yl]carbonylpyrrolidine-2-carboxamide.]]  
propanoyl]pyrrolidin-2-yl]-carbonylpyrrolidine-2-carboxamide. The  
compound was obtained as a white foamy substance.

5  $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.88\text{--}1.05(1\text{H}, \text{m}), 1.12(9\text{H}, \text{s}),$   
1.29-2.00(10H, m), 2.04(1H, t, J=11.3Hz), 2.25-2.38(2H, m),  
2.42-2.53(1H, m), 2.78-2.88(2H, m), 2.92-3.05(2H, m),  
3.30-3.40(1H, m), 3.50(1H, d, J=14.7Hz), 3.52-3.58(1H, m),  
3.76-3.83(1H, m), 3.81(1H, d, J=14.7Hz), 4.27-4.37(2H, m),  
10 4.57(1H, d, J=6.9Hz), 7.13-7.33(16H, m)  
FAB-MS(m/e, as  $(\text{C}_{41}\text{H}_{52}\text{N}_4\text{O}_4+\text{H})^+$ ): 665

#### Example 46

(2R)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-  
15 pyrrolidin-2-yl]carbonyl-N-((3S)-3-piperidylmethyl)pyrrolidine-2-  
carboxamide

To 1.65 g of (2R)-1-((2S,4R)-4-tert-butoxy-1-(3,3,3-  
triphenylpropanoyl)pyrrolidin-2-yl]carbonyl-N-((3S)-3-  
piperidylmethyl)pyrrolidine-2-carboxamide, 5 ml of trifluoroacetic  
20 acid was added at room temperature, followed by 1 hour's stirring at  
the same temperature. The reaction liquid was distilled off under  
reduced pressure, diluted with chloroform, rendered basic with 4N  
aqueous sodium hydroxide solution, extracted with chloroform and  
dried over anhydrous sodium sulfate. Distilling the solvent off under  
25 reduced pressure, 1.56 g of the title compound was obtained as a  
white foamy substance.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.93\text{--}1.08(1\text{H}, \text{m}), 1.32\text{--}1.50$   
(1H, m), 1.50-2.05(10H, m), 2.09(1H, t, J=11.1Hz),  
2.23-2.32(1H, m), 2.51(1H, dt, J=2.3, 9.6Hz), 2.57-2.68  
30 (1H, m), 2.74(1H, d, J=10.9Hz), 2.85-3.02(3H, m), 3.30-3.33  
(1H, m), 3.42(1H, d, J=14.6Hz), 3.58(1H, dd, J=4.1, 11.0Hz),  
3.80-3.87(1H, m), 3.90(1H, d, J=14.6Hz), 4.30-4.38(2H, m),  
4.56(1H, d, J=6.9Hz), 7.17-7.32(16H, m)



FAB-MS(m/e, as (C<sub>37</sub>H<sub>44</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 609

Example 47

(2R)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-pyrrolidin-2-yl)carbonyl-N-(((3R)-1-(2-methylbutyl)-3-piperidyl)-methyl)pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Step 3 of Example 17, using (2R)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-N-((3S)-3-piperidyl-methyl)pyrrolidine-2-carboxamide and 2-methylbutanal. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.80-2.15(24H, m), 2.23-2.35 (1H, m), 2.57-2.82(4H, m), 3.03-3.18(1H, m), 3.30-3.44(2H, m), 3.55-3.70(1H, m), 3.80-4.00(2H, m), 4.29-4.40(2H, m), 4.54-4.63(1H, m), 7.18-7.43(16H, m)

FAB-MS(m/e, as (C<sub>42</sub>H<sub>54</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 679

Example 48

(2R)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-pyrrolidin-2-yl)carbonyl-N-(((3R)-1-methyl-3-piperidyl)methyl)-pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Example 47, using 37% aqueous formaldehyde solution. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.72-0.95(3H, m), 1.23-1.32(3H, m), 1.43(1H, t, J=11.0Hz), 1.51-2.08(6H, m), 2.25(3H, s), 2.20-2.34(1H, m), 2.60-2.86(4H, m), 2.96-3.10(1H, m), 3.28-3.37(1H, m), 3.39(1H, d, J=14.3Hz), 3.59 (1H, dd, J=3.7, 11.1Hz), 3.80-3.91(1H, m), 3.98 (1H, d, J=14.3Hz), 4.26-4.38(2H, m), 4.55(1H, d, J=7.0Hz), 7.15-7.40(16H, m)

FAB-MS(m/e, as (C<sub>38</sub>H<sub>46</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 623

Example 49

(2R)-N-(((3R)-1-ethyl-3-piperidyl)methyl)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl pyrrolidine-2-carboxamide

5           The title compound was prepared by a method similar to Example 47, using acetaldehyde. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.88(3H, t, J=6.7Hz), 1.03  
(2H, t, J=7.3Hz), 1.23-1.30(1H, m), 1.38(1H, t, J=11.0Hz),  
10           1.52-2.03(11H, m), 2.25-2.41(2H, m), 2.14-2.92(3H, m),  
2.99-3.09(1H, m), 3.31-3.36(1H, m), 3.38(1H, d, J=14.3Hz),  
3.57-3.62(1H, m), 3.82-3.91(1H, m), 3.97(1H, d, J=14.3Hz),  
4.28-4.36(2H, m), 4.56(1H, d, J=6.6Hz), 7.17-7.38(16H, m)  
FAB-MS(m/e, as (C<sub>39</sub>H<sub>48</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 637

15

Example 50

(2R)-N-(((3R)-1-butyl-3-piperidyl)methyl)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-pyrrolidine-2-carboxamide

20           The title compound was prepared by a method similar to Example 47, using n-butylaldehyde. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.91(6H, t, J=7.3Hz), 1.25-2.05  
(14H, m), 2.23-2.35(3H, m), 2.63-2.90(4H, m), 3.00-3.10  
25           (1H, m), 3.31-3.36 (1H, m), 3.38(1H, d, J=14.3Hz), 3.59  
(1H, dd, J=4.2, 11.0Hz), 3.81-3.90(1H, m), 3.95  
(1H, d, J=14.3Hz), 4.29-4.38(2H, m), 4.56  
(1H, dd, J=1.3, 6.4Hz), 7.17-7.35(16H, m)  
FAB-MS(m/e, as (C<sub>41</sub>H<sub>52</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 665

30

Example 51

(2R)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-pyrrolidin-2-yl)carbonyl-N-(((3R)-1-pentyl-3-piperidyl)methyl)-

pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Example 47, using valeraldehyde. The compound was obtained as a white solid.

5  $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.83\text{-}2.05(22\text{H}, \text{m}), 2.22\text{-}2.33$   
(3H, m), 2.66-2.81(3H, m), 2.83-2.90(1H, m), 2.99-3.10  
(1H, m), 3.30-3.36(1H, m), 3.39(1H, d,  $J=14.2\text{Hz}$ ), 3.60  
(1H, dd,  $J=3.6, 10.9\text{Hz}$ ), 3.83-3.89(1H, m), 3.95  
(1H, d,  $J=14.2\text{Hz}$ ), 4.28-4.36(2H, m), 4.56  
10 (1H, d,  $J=6.3\text{Hz}$ ), 7.17-7.34(16H, m)  
FAB-MS( $m/e$ , as  $(\text{C}_{42}\text{H}_{54}\text{N}_4\text{O}_4+\text{H})^+$ ): 679

Example 52

15 (2R)-N-(((3R)-1-hexyl-3-piperidyl)methyl)-1-((2S, 4R)-4-  
hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-  
pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Example 47, using n-hexanal. The compound was obtained as a white solid.

20  $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.78\text{-}0.93(6\text{H}, \text{m}), 1.15\text{-}2.10$   
(18H, m), 2.20-2.35(3H, m), 2.54-2.65(1H, m), 2.70-2.80  
(2H, m), 2.80-2.91(1H, m), 3.02-3.12(1H, m), 3.30-3.40(1H, m),  
3.40(1H, d,  $J=14.5\text{Hz}$ ), 3.59(1H, dd,  $J=3.8, 11.1\text{Hz}$ ), 3.85  
(1H, dt,  $J=2.6, 10.4\text{Hz}$ ), 3.94(1H, d,  $J=14.5\text{Hz}$ ), 4.29-4.38  
25 (2H, m), 4.53-4.60(1H, m), 7.17-7.38(16H, m)  
FAB-MS( $m/e$ , as  $(\text{C}_{43}\text{H}_{56}\text{N}_4\text{O}_4+\text{H})^+$ ): 693

Example 53

30 (2R)-N-(((3R)-1-cycloheptylmethyl-3-piperidyl)methyl)-1-((2S,  
4R)-4- hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-  
pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Example 47, using cycloheptanecarbaldehyde. The compound was

obtained as a white foamy substance.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm})$ : 0.75-0.90(1H, m), 1.02-2.07  
(27H, m), 2.25-2.33(1H, m), 2.49-2.68(2H, m), 2.70-2.80  
(2H, m), 3.03-3.14(1H, m), 3.30-3.40(1H, m), 3.40  
(1H, d,  $J=14.5\text{Hz}$ ), 3.60(1H, dd,  $J=3.9, 11.2\text{Hz}$ ), 3.80-3.87  
5 (1H, m), 3.90(1H, d,  $J=14.5\text{Hz}$ ), 4.29-4.40(2H, m), 4.57  
(1H, d,  $J=6.6\text{Hz}$ ), 7.14-7.37(16H, m)  
FAB-MS( $m/e$ , as  $(\text{C}_{45}\text{H}_{58}\text{N}_4\text{O}_4+\text{H})^+$ ): 719

#### 10 Example 54

(2R)-N-(((3R)-1-ethyl-3-piperidyl)methyl)-1-((2S, 4R)-4-  
hydroxy-1-(3,3,3-tris(4-chlorophenyl)propanoyl)pyrrolidin-2-yl)-  
carbonylpyrrolidine-2-carboxamide  
(Step 1)

15 Synthesis of (2R)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-tris(4-  
chlorophenyl)propanoyl)pyrrolidin-2-yl)carbonyl-N-((3S)-3-  
piperidylmethyl)pyrrolidine-2-carboxamide

The title compound was prepared by successively conducting  
Step 4 of Example 45 and Example 46, using 3,3,3-tris(4-  
20 chlorophenyl)propionic acid.  
(Step 2)

Synthesis of (2R)-N-(((3R)-1-ethyl-3-piperidyl)methyl)-1-((2S,  
4R)-4-hydroxy-1-(3,3,3-tris(4-chlorophenyl)propanoyl)pyrrolidin-2-yl)-  
carbonylpyrrolidine-2-carboxamide

25 The title compound was prepared by a method similar to  
Step 3 of Example 17, using (2R)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-tris-  
(4-chlorophenyl)propanoyl)pyrrolidin-2-yl)carbonyl-N-((3S)-3-  
piperidylmethyl)pyrrolidine-2-carboxamide and acetaldehyde. The  
compound was obtained as a white foamy substance.

30  $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm})$ : 0.80-1.78(12H, m), 1.90-2.08  
(5H, m), 2.26-2.40(3H, m), 2.52-2.63(1H, m), 2.73-2.96  
(3H, m), 3.00-3.11(1H, m), 3.34(1H, d,  $J=15.1\text{Hz}$ ), 3.35-3.42  
(1H, m), 3.60-3.68 (1H, m), 3.84(1H, d,  $J=15.1\text{Hz}$ ), 3.83-3.90

(1H, m), 4.35-4.48 (2H, m), 4.56(1H, dd, J=1.4,7.4Hz),  
7.12-7.30(12H,m)

FAB-MS(m/e, as (C<sub>39</sub>H<sub>45</sub>Cl<sub>3</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 739

5 Example 55

(2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-pyrrolidine-2-carboxamide

(Step 1)

10 Synthesis of (2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)-methyl)pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Steps 2-4 of Example 17, using (2R)-1-benzyloxycarbonyl-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)pyrrolidine-2-carboxamide.

15

(Step 2)

Synthesis of (2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

20 The title compound was prepared by successively conducting methods similar to Steps 1-2 of Example 17, Step 3 of Example 1 and Step 4 of Example 17, using (2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)pyrrolidine-2-carboxamide and N-(tert-butoxycarbonyl)-O-benzyl-trans-4-hydroxy-L-proline. The compound was  
25 obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.80-2.02(24H, m), 2.05  
(2H, d, J=7.0Hz), 2.25-2.35(1H, m), 2.52-2.80(4H, m),  
3.04-3.13(1H, m), 3.30-3.38(1H,m), 3.39(1H, d, J=14.5Hz),  
3.60(1H, dd, J=3.8,11.0Hz), 3.81-3.89(1H, m), 3.91  
30 (1H, d, J=14.5Hz), 4.30-4.38(2H, m), 4.57 (1H, d, J=6.6Hz),  
7.17-7.33(16H, m)

FAB-MS(m/e, as (C<sub>44</sub>H<sub>56</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 705

Example 56

(2R)-N-((1-cyclohexylmethyl-3-piperidyl)methyl)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-pyrrolidine-2-carboxamide

5           The title compound was prepared by successively conducting a method similar to Exampe 55, using 3-aminomethyl-1-(tert-butoxy-carbonyl)piperidine. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.73-2.20(26H, m), 2.23-2.34  
(1H, m), 2.53-2.90(4H, m), 2.97-3.13(1H, m), 3.29-3.43(2H, m),  
10           3.53-3.70(1H, m), 3.80-3.95(2H, m), 4.27-4.40(2H, m),  
4.52-4.60(1H, m), 7.15-7.40(16H, m)

FAB-MS(m/e, as (C<sub>44</sub>H<sub>56</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 705

Example 57

15           (2R)-1-((2S, 4S)-4-amino-1-(3,3,3-triphenylpropanoyl)-pyrrolidin-2-yl)carbonyl-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)-methyl)pyrrolidine-2-carboxamide  
(Step 1)

Synthesis of (2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)-  
20 methyl)-1-((2S, 4R)-4-(methylsulfonyloxy)-1-(3,3,3-triphenylpropanoyl) pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

To a solution of 30 mg of (2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide in 0.6  
25 ml of chloroform, 0.018 ml of triethylamine and 0.004 ml of methanesulfonyl chloride were added under cooling with ice, followed by 50 minutes' stirring at room temperature. The reaction liquid was diluted with chloroform, washed with saturated aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate.  
30 Distilling the solvent off under reduced pressure, the resultant residue was purified by means of a preparative thin-layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art 5744 (Merck), chloroform/methanol/28% aqueous ammonia = 100/10/1) to provide 33

mg of the title compound.

(Step 2)

Synthesis of (2R)-1-((2S, 4S)-4-azido-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)pyrrolidine-2-carboxamide

To a solution of 33 mg of (2R)-N-(((3R)-1-[[cyclohexylmethyl]-3-piperidyl)methyl]-1-((2S, 4R)-4-(methylsulfonyloxy)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide in 1 ml of N,N-dimethylformamide, 8.3 mg of sodium azide was added at room temperature, followed by 10 hours' stirring at 85°C under heating. The reaction liquid was diluted with ethyl acetate, washed with water and dried over anhydrous sodium sulfate. Distilling the solvent off under reduced pressure, the resultant residue was purified by means of a preparative thin-layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art 5744 (Merck), chloroform/methanol/28% aqueous ammonia = 100/10/1) to provide 25 mg of the title compound.

(Step 3)

Synthesis of (2R)-1-((2S, 4S)-4-amino-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)pyrrolidine-2-carboxamide

To a solution of 24 mg of (2R)-1-((2S, 4S)-4-azido-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)pyrrolidine-2-carboxamide in 0.5 ml of 20% hydrous tetrahydrofuran, 13 mg of triphenylphosphine was added at room temperature, followed by 3 hours' refluxing under heating. The reaction liquid was diluted with chloroform, washed with saturated aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate. Distilling the solvent off under reduced pressure, the resultant residue was purified by means of a preparative thin-layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art 5744 (Merck), chloroform/methanol/28% aqueous ammonia = 90/10/1) to provide 16 mg of the title compound in the form of a

white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.75-0.95(4H, m), 1.10-1.32(4H, m),  
1.39(1H, t, J=10.8Hz), 1.40-2.01(15H, m), 2.06  
(2H, d, J=6.9Hz), 2.07-2.18(1H, m), 2.26-2.33(1H, m), 2.54  
5 (1H, quint, J=6.5Hz), 2.60-2.70(1H, m), 2.70-2.80(1H, m),  
2.89-2.99(1H, m), 3.05-3.17(3H, m), 3.29-3.37(1H, m),  
3.39(1H, d, J=14.3Hz), 3.76-3.82(1H, m), 3.89  
(1H, d, J=14.3Hz), 4.13(1H, t, J=6.6Hz), 4.59  
(1H, dd, J=1.5, 8.0Hz), 7.13-7.32(16H, m)  
10 FAB-MS(m/e, as (C<sub>44</sub>H<sub>57</sub>N<sub>5</sub>O<sub>3</sub>+H)<sup>+</sup>): 704

#### Example 58

(2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-1-((2S,  
4S)-4-dimethylamino-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)-  
15 carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
Step 3 of Example 17, using (2R)-1-((2S, 4S)-4-amino-1-(3,3,3-  
triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-N-(((3R)-1-cyclohexyl-  
methyl-3-piperidyl)methyl)pyrrolidine-2-carboxamide and 37%  
20 aqueous formaldehyde solution. The compound was obtained as a  
white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.78-0.92(4H, m), 1.10-1.27(4H, m),  
1.34-2.00(16H, m), 2.04(2H, d, J=7.2Hz), 2.08(6H, s),  
2.27-2.35(1H, m), 2.60-2.84(4H, m), 3.05-3.17(2H, m),  
25 3.27-3.32(1H, m), 3.33(1H, d, J=14.0Hz), 3.78-3.86(1H, m),  
3.90(1H, d, J=14.0Hz), 4.05-4.13(1H, m), 4.59  
(1H, d, J=6.6Hz), 7.16-7.34(16H, m)  
FAB-MS(m/e, as (C<sub>46</sub>H<sub>61</sub>N<sub>5</sub>O<sub>3</sub>+H)<sup>+</sup>): 732

#### 30 Example 59

(2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-1-((2S,  
4S)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)-  
carbonylpyrrolidine-2-carboxamide



The title compound was prepared by a method similar to Steps 3-4 of Example 45, using (2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)pyrrolidine-2-carboxamide and N-benzyloxy-carbonyl-cis-4-hydroxy-L-proline. The compound was obtained as a white foamy substance.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.78\text{-}0.93(5\text{H}, \text{m}), 1.10\text{-}1.33(5\text{H}, \text{m}), 1.43(1\text{H}, \text{t}, J=10.6\text{Hz}), 1.40\text{-}2.01(12\text{H}, \text{m}), 2.06(2\text{H}, \text{d}, J=7.2\text{Hz}), 2.27\text{-}2.35(1\text{H}, \text{m}), 2.53\text{-}2.70(3\text{H}, \text{m}), 2.71\text{-}2.81(1\text{H}, \text{m}), 3.07\text{-}3.18(1\text{H}, \text{m}), 3.40(1\text{H}, \text{d}, J=14.1\text{Hz}), 3.40\text{-}3.49(2\text{H}, \text{m}), 3.88\text{-}3.95(1\text{H}, \text{m}), 3.94(1\text{H}, \text{d}, J=14.1\text{Hz}), 4.07\text{-}4.16(1\text{H}, \text{m}), 4.19(1\text{H}, \text{d}, J=7.5\text{Hz}), 4.59(1\text{H}, \text{d}, J=6.2\text{Hz}), 5.62(1\text{H}, \text{d}, J=11.9\text{Hz}), 7.10(1\text{H}, \text{t}, J=5.9\text{Hz}), 7.14\text{-}7.38(15\text{H}, \text{m})$

FAB-MS(m/e, as  $(\text{C}_{44}\text{H}_{56}\text{N}_4\text{O}_4+\text{H})^+$ ): 705

#### Example 60

(2R)-1-((2S, 4R)-4-amino-1-(3,3,3-triphenylpropanoyl)-pyrrolidin-2-yl)carbonyl-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Example 57 using (2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-1-((2S, 4S)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide. The compound was obtained as a white solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.73\text{-}2.10(27\text{H}, \text{m}), 2.25\text{-}2.34(1\text{H}, \text{m}), 2.47\text{-}2.69(3\text{H}, \text{m}), 2.69\text{-}2.80(1\text{H}, \text{m}), 3.10(1\text{H}, \text{quint}, J=6.7\text{Hz}), 3.29\text{-}3.37(1\text{H}, \text{m}), 3.42(1\text{H}, \text{d}, J=14.6\text{Hz}), 3.59\text{-}3.70(2\text{H}, \text{m}), 3.79\text{-}3.85(1\text{H}, \text{m}), 3.90(1\text{H}, \text{d}, J=14.6\text{Hz}), 4.30(1\text{H}, \text{t}, J=7.3\text{Hz}), 4.58(1\text{H}, \text{dd}, J=1.6, 7.8\text{Hz}), 7.13\text{-}7.37(16\text{H}, \text{m})$

FAB-MS(m/e, as  $(\text{C}_{44}\text{H}_{57}\text{N}_5\text{O}_3+\text{H})^+$ ): 704

#### Example 61

(2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-1-((2S, 4R)-4-dimethylamino-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)-carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
5 Example 58, using (2R)-1-((2S, 4R)-4-amino-1-(3,3,3-triphenylpropanoyl)-pyrrolidin-2-yl)carbonyl-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)pyrrolidine-2-carboxamide.  
The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.75-0.92(4H, m), 1.10-1.30  
10 (4H, m), 1.30-1.75(13H, m), 1.75-1.97(2H, m), 2.04  
(2H, d, J=7.2Hz), 2.12(6H, s), 2.24-2.36(1H, m), 2.37-2.50  
(1H, m), 2.57-2.69(2H, m), 2.70-2.80(1H, m), 3.02-3.15(2H, m),  
3.28-3.38(1H, m), 3.44(1H, d, J=14.7Hz), 3.50-3.60(1H, m),  
3.71-3.80(1H, m), 3.88(1H, d, J=14.7Hz),  
15 4.24(1H, d, J=8.6Hz), 4.58(1H, d, J=6.5Hz), 7.05  
(1H, t, J=5.3Hz), 7.15-7.32(15H, m)  
FAB-MS(m/e, as (C<sub>46</sub>H<sub>61</sub>N<sub>5</sub>O<sub>3</sub>+H)<sup>+</sup>): 732

#### Example 62

20 N-(7-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)amino-7-oxoheptyl)-3,3,3-triphenylpropanamide

The title compound was prepared by successively conducting  
methods similar to Examples 24 and 28, using 7-((tert-butoxy-  
carbonyl)amino)heptanoic acid. The compound was obtained as a  
25 white foamy substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.78-1.82(26H, m), 2.10  
(2H, d, J=7.5Hz), 2.17(2H, d, J=6.9Hz), 2.68-2.80(2H, m),  
2.83-2.95(2H, m), 3.08-3.29(2H, m), 3.56(2H, s), 4.74-4.83  
(1H, m), 5.85-6.00(1H, m), 7.10-7.40(15H, m)  
30 FAB-MS(m/e, as (C<sub>41</sub>H<sub>55</sub>N<sub>3</sub>O<sub>2</sub>+H)<sup>+</sup>): 622

#### Example 63

(2R)-N-(1-cyclohexylmethyl-4-piperidyl)-1-((2S)-1-(3,3,3-

triphenylpropanoyl)pyrrolidin-2-yl}carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Step 5 of Example 1, using 1-cyclohexylmethyl-4-piperidinamine (JP 52122378) and (2R)-1-{(2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonylpyrrolidine-2-carboxylic acid. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.70-0.92(3H, m), 1.00-1.20(3H, m), 1.22-1.39(3H, m), 1.40-1.93(14H, m), 1.95-2.05(1H, m), 2.07-2.92(2H, m), 2.20-2.29(1H, m), 2.33-2.42(1H, m), 2.80-2.92(2H, m), 3.28-3.35(2H, m), 3.36(1H, d, J=13.7Hz), 3.62-3.78(1H, m), 3.85-3.89(1H, m), 3.90(1H, d, J=13.7Hz), 4.09(1H, t, J=6.7Hz), 4.53(1H, d, J=7.9Hz), 6.86(1H, d, J=8.4Hz), 7.13-7.38(15H, m)

FAB-MS(m/e, as (C<sub>43</sub>H<sub>54</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 675

Example 64

(2R)-N-(4-piperidylmethyl)-1-{(2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonylpyrrolidine-2-carboxamide

The title compound was obtained by successively conducting methods similar to Example 63 and Step 2 of Example 17, using 4-aminomethyl-1-(tert-butoxycarbonyl)piperidine which was synthesized by the method of J. D. Prugh, et al. [*Synth. Commun.*, Vol. 22, 2357-2360 (1992)]. The compound was obtained as a pale yellow oily substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.90-2.05(13H, m), 2.27-2.38(1H, m), 2.48-2.60(2H, m), 2.62-2.84(2H, m), 2.98-3.10(3H, m), 3.28-3.40(2H, m), 3.43(1H, d, J=14.7Hz), 3.75-3.83(1H, m), 3.84(1H, d, J=14.7Hz), 4.09-4.14(1H, m), 4.57-4.62(1H, m), 7.15-7.32(16H, m)

FAB-MS(m/e, as (C<sub>37</sub>H<sub>44</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 593

Example 65

(2R)-N-((1-cyclohexylmethyl-4-piperidyl)methyl)-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
5 Step 3 of Example 17, using (2R)-N-(4-piperidylmethyl)-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide. The compound was obtained as a colorless oily substance.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD, δppm): 0.85-1.83(20H, m), 1.85-2.00  
10 (4H, m), 2.01-2.12(2H, m), 2.15-2.22(2H, m), 2.63-2.73  
(1H, m), 2.81-3.01(4H, m), 3.37-3.53(2H, m), 3.53  
(1H, d, J=15.0Hz), 3.78-3.86(1H, m), 3.90(1H, d, J=15.0Hz),  
4.22(1H, t, J=7.4Hz), 4.37-4.43(1H, m), 7.13-7.31(15H, m)  
FAB-MS(m/e, as (C<sub>44</sub>H<sub>56</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 689

15

Example 66

(2R)-N-{2-(4-piperidyl)ethyl}-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
20 Example 64, using 4-aminoethyl-1-(tert-butoxycarbonyl)piperidine which was synthesized by the method of B.C. Askew, et al. [*J. Med. Chem.*, Vol. 40, 1779-1788 (1997)]. The compound was obtained as a white foamy substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.98-1.12(2H, m), 1.22-1.70  
25 (7H, m), 1.72-2.00(6H, m), 2.25-2.34(1H, m), 5.08  
(2H, dt, J=1.8, 12.0Hz), 2.69-2.88(2H, m), 2.97-3.08(2H, m),  
3.12-3.42(3H, m), 3.44(1H, d, J=14.8Hz), 3.76-4.01(1H, m),  
3.86(1H, d, J=14.8Hz), 4.14(1H, t, J=6.9Hz), 4.58  
(1H, d, J=7.7Hz), 7.12-7.30(16H, m)  
30 FAB-MS(m/e, as (C<sub>38</sub>H<sub>46</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 607

Example 67

(2R)-N-{2-(1-cyclohexylmethyl-4-piperidyl)ethyl}-1-((2S)-1-

(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Step 3 of Example 17, using (2R)-N-{2-(4-piperidyl)ethyl}-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonylpyrrolidine-2-carboxamide. The compound was obtained as a colorless oily substance.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD, δppm): 0.83-1.82(22H, m), 1.85-2.00 (4H, m), 2.01-2.10(2H, m), 2.15-2.21(2H, m), 2.64-2.77 (1H, m), 2.86-3.00 (3H, m), 3.10-3.22(1H, m), 3.38-3.50 (2H, m), 3.54(1H, d, J=15.3Hz), 3.76-3.84(1H, m), 3.91 (1H, d, J=15.3Hz), 1.22(1H, t, J=7.3Hz), 4.38-4.42(1H, m), 7.13-7.32(15H, m)

FAB-MS(m/e, as (C<sub>45</sub>H<sub>58</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 703

Example 68

N-{3-(2-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)amino-2-oxoethyl)amino-3-oxopropyl}-3,3,3-triphenylpropanamide  
(Step 1)

Synthesis of 2-amino-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)acetamide

The title compound was prepared by conducting procedures similar to Steps 1-2 of Example 17, using (3R)-3-aminomethyl-1-(cyclohexylmethyl)piperidine and (tert-butoxycarbonyl)-glycine.

(Step 2)

Synthesis of N-{3-(2-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)amino-2-oxoethyl)amino-3-oxopropyl}-3,3,3-triphenylpropanamide

The title compound was prepared by successively conducting procedures similar to Steps 1-2 of Example 17 and Step 4 of Example 45, using 2-amino-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-acetamide and N-(tert-butoxycarbonyl)-β-alanine. The compound was obtained as a white foamy substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.78-2.08(22H, m), 2.54-2.64  
(2H,m), 3.14-3.27(4H, m), 3.56(2H, s), 3.75(2H, d, J=5.3Hz),  
5.88-5.95(2H, m), 6.39-6.42(1H, m), 7.16-7.31(15H, m)  
FAB-MS(m/e, as (C<sub>39</sub>H<sub>50</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 623

5

#### Example 69

(2R,4S)-N-{(1-cyclohexylmethyl-3-piperidyl)methyl}-4-  
hydroxy-1-{(2S,4R)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}-  
carbonylpyrrolidine-2-carboxamide

10 (Step 1)

Synthesis of (2R,4S)-N-{(1-cyclohexylmethyl-3-piperidyl)-  
methyl}-4-hydroxypyrrolidine-2-carboxamide monohydrochloride

The title compound was prepared by conducting a method  
similar to Steps 5-6 of Example 1, using 3-aminomethyl-1-  
15 (cyclohexylmethyl)piperidine and N-(tert-butoxycarbonyl)-trans-4-  
hydroxy-D-proline.

(Step 2)

Synthesis of (2R,4S)-N-{(1-cyclohexylmethyl-3-piperidyl)-  
methyl}-4-hydroxy-1-{(2S,4R)-1-(3,3,3-triphenylpropanoyl)-  
20 pyrrolidin-2-yl}carbonylpyrrolidine-2-carboxamide

The title compound was prepared by successively conducting  
procedures similar to Steps 1-3 of Example 1, using (2R, 4S)-N-{(1-  
cyclohexylmethyl-3-piperidyl)methyl}pyrrolidine-2-carboxamide  
monohydrochloride and N-(tert-butoxycarbonyl)-L-proline. The  
25 product was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.75-0.96(3H, m), 1.08-1.32  
(4H, m), 1.38-2.20(19H, m), 2.30-2.43(1H, m), 2.56-2.85  
(4H, m), 2.93-3.15(1H, m), 3.25-3.32(1H, m), 3.38-3.43  
(2H, m), 3.85-3.93(2H, m), 4.00-4.10(1H, m), 4.38-4.49  
30 (1H, m), 4.65(1H, dd, J=4.4,8.2Hz), 7.13-7.33(16H, m)

FAB-MS(m/e, as (C<sub>44</sub>H<sub>56</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 705

#### Example 70

(2R, 4S)-N-{(1-cyclohexylmethyl-3-piperidyl)methyl}-1-{(2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonyl-4-hydroxypyrrolidine-2-[[carboxamide]] carboxamide

The title compound was prepared by a method similar to  
5 Step 2 of Example 55, using (2R, 4S)-N-{(1-cyclohexylmethyl-3-piperidyl)methyl}-4-hydroxypyrrolidine-2-carboxamide monohydrochloride. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.70-0.94(3H, m), 1.08-1.32  
(4H, m), 1.39-2.13(17H, m), 2.14-2.23(2H, m), 2.42-2.53  
10 (1H, m), 2.57-2.70(1H, m), 2.72-2.88(2H, m), 2.88-3.08(1H, m),  
3.31-3.48(2H, m), 3.56-3.62(1H, m), 3.68-3.90(2H, m),  
4.27-4.39(3H, m), 4.52-4.60  
(1H,m),7.13-7.30(16H,m)

FAB-MS(m/e, as (C<sub>44</sub>H<sub>56</sub>N<sub>4</sub>O<sub>5</sub>+H)<sup>+</sup>): 721

15

#### Example 71

(2R)-1-{(2S, 4S)-4-acetoxy-1-(3,3,3-triphenylpropanoyl)-pyrrolidin-2-yl}carbonyl-N-{((3R)-1-cyclohexylmethyl-3-piperidyl)-methyl}pyrrolidine-2-carboxamide

20 A solution of 40 mg of (2R)-N-{((3R)-1-cyclohexylmethyl-3-piperidyl)methyl}-1-{(2S, 4R)-4-(methylsulfonyloxy)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonylpyrrolidine-2-carboxamide and 30 mg of tetrabutylammonium acetate in 1 ml of N,N-dimethylformamide was stirred at 85°C for 15 hours under  
25 heating. The reaction liquid was diluted with ethyl acetate, successively washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified with a preparative thin-layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art. 5744  
30 (Merck), chloroform/methanol/28% aqueous ammonia = 100/8/1), to provide 14 mg of the title compound as a colorless oily substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.78-2.10(26H, m), 2.20-2.30  
(1H, m), 2.32-2.50(2H, m), 2.60-2.68(1H, m), 2.73-3.08(4H, m),

3.30-3.40 (1H,m), 3.40(1H, d, J=14.6Hz), 3.56-3.70(1H, m),  
3.72-3.80 (1H, m), 4.00(1H, d, J=14.6Hz), 4.25-4.33(2H, m),  
4.52-4.56(1H, m), 7.13-7.45(16H, m)

FAB-MS(m/e, as (C<sub>46</sub>H<sub>58</sub>N<sub>4</sub>O<sub>5</sub>+H)<sup>+</sup>): 747

5

#### Example 72

(2R)-1-((2S, 4R)-4-acetoxy-1-(3,3,3-triphenylpropanoyl)-  
pyrrolidin-2-yl)carbonyl-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)  
methyl)pyrrolidine-2-carboxamide

10       The title compound was prepared by successively conducting  
procedures similar to Step 1 of Example 57 and Example 71, using  
(2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-1-((2S, 4S)-4-  
hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-  
pyrrolidine-2-carboxamide. The compound was obtained as a yellow  
15   oily substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.70-0.98(4H, m), 1.10-1.38(4H, m),  
1.32(1H, t, J=10.7Hz), 1.39-2.20(15H, m), 2.05  
(3H, s), 2.27-2.38 (2H, m), 2.55-2.65(1H, m), 2.68-2.80  
(1H, m), 2.98-3.18(3H, m), 3.31-3.40(1H, m), 3.44  
20   (1H, d, J=15.3Hz), 3.74(1H, dd, J=4.6, 11.5Hz), 3.79-3.84  
(1H, m), 3.85(1H, d, J=15.3Hz), 4.35(1H, t, J=8.0Hz), 4.59  
(1H, d, J=6.6Hz), 5.20-5.27(1H, m), 7.14-7.32(16H, m)

FAB-MS(m/e, as (C<sub>46</sub>H<sub>58</sub>N<sub>4</sub>O<sub>5</sub>+H)<sup>+</sup>): 747

#### 25   Example 73

N-((1-cyclohexylmethyl-3-piperidyl)methyl)-1-(1-(3,3,3-  
triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-  
carboxamide

30       The title compound was prepared by successively conducting  
procedures similar to Examples 41 and 44, using methyl pyrrolidine-  
2-carboxylate monohydrochloride and N-(tert-butoxycarbonyl)-  
DL-proline. The compound was obtained as a colorless oily  
substance.



$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.60\text{-}1.12(3\text{H}, \text{m}), 1.15\text{-}2.20$   
 $(24\text{H}, \text{m}), 2.24\text{-}2.38(1\text{H}, \text{m}), 2.46\text{-}2.90(3\text{H}, \text{m}), 2.98\text{-}3.19$   
 $(1\text{H}, \text{m}), 3.20\text{-}4.65(8\text{H}, \text{m}), 7.10\text{-}8.20(16\text{H}, \text{m})$   
 $\text{FAB-MS}(\text{m/e}, \text{as } (\text{C}_{44}\text{H}_{56}\text{N}_4\text{O}_3+\text{H})^+): 689$

5

#### Example 74

(2R)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-  
pyrrolidin-2-yl)carbonyl-N-(((3R)-1-propyl-3-piperidyl)methyl)-  
pyrrolidine-2-carboxamide

10        The title compound was prepared by a method similar to  
Example 47, using propionaldehyde. The compound was obtained as  
a white solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.80\text{-}2.06(18\text{H}, \text{m}), 2.20\text{-}2.32$   
 $(3\text{H}, \text{m}), 2.67(1\text{H}, \text{d}, J=11.4\text{Hz}), 2.72\text{-}2.82(2\text{H}, \text{m}), 2.83\text{-}2.93$   
15         $(1\text{H}, \text{m}), 2.96\text{-}3.08(1\text{H}, \text{m}), 3.30\text{-}3.36(1\text{H}, \text{m}), 3.39$   
 $(1\text{H}, \text{d}, J=14.2\text{Hz}), 3.61(1\text{H}, \text{dd}, J=3.6, 11.2\text{Hz}), 3.81\text{-}3.90$   
 $(1\text{H}, \text{m}), 3.96(1\text{H}, \text{d}, J=14.2\text{Hz}), 4.28\text{-}4.37(2\text{H}, \text{m}), 4.56$   
 $(1\text{H}, \text{d}, J=8.0\text{Hz}), 7.17\text{-}7.38(16\text{H}, \text{m})$   
 $\text{ESI-MS}(\text{m/e}, \text{as } (\text{C}_{40}\text{H}_{50}\text{N}_4\text{O}_4+\text{H})^+): 651$

20

#### Example 75

(2R)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-  
pyrrolidin-2-yl)carbonyl-N-(((3R)-1-octyl-3-piperidyl)methyl)-  
pyrrolidine-2-carboxamide

25        The title compound was prepared by a method similar to  
Example 47, using n-octanal. The compound was obtained as a  
white foamy substance.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.83\text{-}0.95(6\text{H}, \text{m}), 1.20\text{-}1.83$   
 $(18\text{H}, \text{m}), 1.86\text{-}2.02(4\text{H}, \text{m}), 2.21\text{-}2.32(3\text{H}, \text{m}), 2.64\text{-}2.80$   
30         $(3\text{H}, \text{m}), 2.83\text{-}2.91(1\text{H}, \text{m}), 3.00\text{-}3.10(1\text{H}, \text{m}), 3.31\text{-}3.36$   
 $(1\text{H}, \text{m}), 3.39(1\text{H}, \text{d}, J=14.4\text{Hz}), 3.60(1\text{H}, \text{dd}, J=3.9, 10.9\text{Hz}),$   
 $3.81\text{-}3.90(1\text{H}, \text{m}), 3.95(1\text{H}, \text{d}, J=14.4\text{Hz}), 4.28\text{-}4.37(2\text{H}, \text{m}),$   
 $4.56(1\text{H}, \text{dd}, J=1.6, 7.9\text{Hz}), 7.16\text{-}7.34(16\text{H}, \text{m})$

FAB-MS(m/e, as (C<sub>45</sub>H<sub>60</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 721

Example 76

(2R)-N-{((3R)-1-cyclopropylmethyl-3-piperidyl)methyl}-  
5 1-((2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-  
yl}carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Example 47, using cyclopropanecarbaldehyde. The compound was obtained as a white solid.

10 <sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.04-0.10(2H, m), 0.45-0.53(2H, m),  
88(4H, t, J=6.8Hz), 1.22-1.38(3H, m), 1.42-1.50(1H, m),  
1.55-2.05(6H, m), 2.16-2.32(3H, m), 2.62-2.80(2H, m),  
2.88-2.98 (1H, m), 2.98-3.09(2H, m), 3.30-3.37(1H, m), 3.39  
(1H, d, J=14.2Hz), 3.61(1H, dd, J=3.8, 11.1Hz), 3.82-3.91  
15 (1H, m), 3.97(1H, d, J=14.2Hz), 4.28-4.37(2H, m), 4.53-4.59  
(1H, m), 7.17-7.38(16H, m)

FAB-MS(m/e, as (C<sub>41</sub>H<sub>50</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 663

Example 77

20 (2R)-N-{((3R)-1-allyl-3-piperidyl)methyl}-1-((2S, 4R)-4-  
hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}-  
carbonylpyrrolidine-2-carboxamide

To a solution of 37 mg of (2R)-N-((3S)-3-piperidylmethyl)-1-  
{(2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonylpyrrolidine-  
25 2-carboxamide in 0.9 ml of acetonitrile, 0.0055 ml of allyl bromide and  
25 mg of potassium carbonate were added at room temperature,  
followed by 1.5 hours' stirring at 80°C under heating. The reaction  
liquid was diluted with chloroform, washed successively with water  
and 1N aqueous sodium hydroxide solution, and dried over anhydrous  
30 sodium sulfate. After distilling the solvent off under reduced  
pressure, the resulting residue was purified with a preparative  
thin-layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art 5744 (Merck),  
chloroform/methanol/28% aqueous ammonia = 100/10/1), to provide

23 mg of the title compound as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.80-2.10(15H, m), 2.24-2.33  
(1H, m), 2.62-2.72(1H, m), 2.73-2.82(1H, m), 2.83-2.92  
(1H, m), 2.93-2.9(1H, m), 3.00-3.10(1H, m), 3.30-3.36  
(1H, m), 3.39(1H, d, J=14.1Hz), 3.58-3.66(1H, m), 3.80-3.90  
(1H, m), 3.95(1H, d, J=14.1Hz), 4.28-4.37(2H, m), 4.52-4.58  
(1H, m), 5.07-5.19(2H, m), 5.82-5.96(1H, m),  
7.17-7.38(16H, m)

FAB-MS(m/e, as (C<sub>40</sub>H<sub>48</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 649

#### Example 78

(2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-1-  
((2S, 4R)-4-hydroxy-1-(2-methyl-3,3,3-triphenylpropanoyl)-  
pyrrolidin-2-yl}carbonylpyrrolidine-2-carboxamide

The title compound was prepared by successively conducting procedures similar to Step 4 of Example 45, Example 46 and Step 3 of Example 17, using 2-methyl-3,3,3-triphenylpropionic acid. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.70-2.40(31H, m), 2.60-2.90  
(2H, m), 2.97-3.10(1H, m), 3.33-3.43(1H, m), 3.76-3.82(1H, m),  
3.87-4.00(2H, m), 4.18-4.57(2H, m), 4.60-4.75(2H, m),  
6.70-6.80(1H, m), 7.10-7.30(15H, m)

FAB-MS(m/e, as (C<sub>45</sub>H<sub>58</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 719

#### Example 79

(2R)-1-((2S, 4S)-4-acetylamino-1-(3,3,3-triphenylpropanoyl)-  
pyrrolidin-2-yl}carbonyl-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)-  
methyl}pyrrolidine-2-carboxamide

To a solution of 22 mg of (2R)-1-((2S, 4S)-4-amino-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonyl-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl}pyrrolidine-2-carboxamide in 1 ml of chloroform, 0.0089 ml of acetic anhydride and 0.0127 ml of pyridine were added at room temperature, followed by an hour's

stirring at the same temperature. The reaction liquid was diluted with chloroform, washed successively with saturated aqueous sodium bicarbonate solution and saturated brine, and dried over anhydrous sodium sulfate. After distilling the solvent off under reduced  
5 pressure, the resulting residue was purified with a preparative thin-layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art 5744 (Merck), chloroform/methanol = 8/1), to provide 18 mg of the title compound as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.78-0.93(4H, m), 1.12-1.86  
10 (17H, m), 1.93(3H, s), 1.94-2.10(4H, m), 2.25-2.33(1H, m), 2.50-2.70(3H, m), 2.73-2.82(1H, m), 3.10-3.27(2H, m), 3.34-3.45(1H, m), 3.39(1H, d, J=14.2Hz), 3.84-3.93(1H, m), 3.88(1H, d, J=14.2Hz), 4.17(1H, d, J=9.3Hz), 4.42-4.51 (1H, m), 4.53-4.60(1H, m), 7.10-7.33(16H, m),  
15 8.00-8.07 (1H, m)  
FAB-MS(m/e, as (C<sub>46</sub>H<sub>59</sub>N<sub>5</sub>O<sub>4</sub>+H)<sup>+</sup>): 746

#### Example 80

(2R)-N-{(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-1-{(2S, 4S)-4-(methylsulfonylamino)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonylpyrrolidine-2-carboxamide  
20

The title compound was prepared by a method similar to Step 1 of Example 57, using (2R)-1-{(2S,4S)-4-amino-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonyl-N-{(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)pyrrolidine-2-carboxamide. The  
25 compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.78-0.97(3H, m), 1.05-2.10 (23H, m), 2.25-2.34(1H, m), 2.53-2.85(3H, m), 2.89(3H, s), 3.07-3.20(1H, m), 3.32-3.55(3H, m), 3.83-4.00(3H, m),  
30 4.15(1H, d, J=8.7Hz), 4.55-4.61(1H, m), 7.03-7.13(1H, m), 7.15-7.40(16H, m)  
FAB-MS(m/e, as (C<sub>45</sub>H<sub>59</sub>N<sub>5</sub>O<sub>5</sub>S+H)<sup>+</sup>): 783

Example 81

(2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-1-  
{(2S)-4-oxo-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonyl-  
pyrrolidine-2-carboxamide

5 To a solution of 0.0037 ml of oxaryl chloride in 0.3 ml of  
dichloromethane, 0.0065 ml of dimethyl sulfoxide was added at  $-78^{\circ}\text{C}$ ,  
followed by 20 minutes' stirring at the same temperature. Then a  
solution of 25 mg of (2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)-  
methyl)-1-  
10 {(2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-  
pyrrolidin-2-yl}carbonylpyrrolidine-2-carboxamide in 0.9 ml of  
dichloromethane was added at the same temperature, followed by 30  
minutes' stirring, addition of 0.0024 ml of triethylamine at the same  
temperature, and 20 minutes' stirring at room temperature. The  
reaction liquid was diluted with chloroform, washed with saturated  
15 brine and dried over anhydrous sodium sulfate. Distilling the  
solvent off under reduced pressure, the resulting residue was purified  
with a preparative thin-layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>,  
Art5744 (Merck); chloroform/methanol = 9/1), to provide 18 mg of the  
title compound as a pale pink solid.

20  $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm})$ : 0.78-2.20(22H, m), 2.21-2.36  
(1H, m), 2.47-2.52(2H, m), 2.55-2.90(3H, m), 2.98-3.20(3H, m),  
3.27-3.55(2H, m), 3.80-4.03(3H, m), 4.50-4.63(2H, m),  
6.88-7.05(1H, m), 7.10-7.40(15H, m)  
FAB-MS(m/e, as  $(\text{C}_{44}\text{H}_{54}\text{N}_4\text{O}_4+\text{H})^+$ ): 703

25

Example 82

(2R)-1-((2S, 3R, 4S)-3,4-dihydroxy-1-(3,3,3-triphenyl-  
propanoyl)pyrrolidin-2-yl)carbonyl-N-((3S)-3-piperidylmethyl)-  
pyrrolidine-2-carboxamide

30 (Step 1)

Synthesis of (2S)-3,4-dehydro-1-(3,3,3-triphenylpropanoyl)-  
pyrrolidine-2-carboxylic acid

The title compound was prepared by successively conducting

procedures similar to Step 1 of Example 24 and Steps 2-4 of Example 1, using N-(tert-butoxycarbonyl)-3,4-dehydro-L-proline.

(Step 2)

Synthesis of (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)-1-((2S)-3,4-dehydro-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Step 4 of Example 45, using (2S)-3,4-dehydro-1-(3,3,3-triphenylpropanoyl)pyrrolidine-2-carboxylic acid and (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)pyrrolidine-2-carboxamide.

(Step 3)

Synthesis of (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)-1-((2S, 3R, 4S)-3,4-dihydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

To a solution of 29 mg of (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)-1-((2S)-3,4-dehydro-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide in 1.5 ml of 33% hydrous acetonitrile, 6 mg of N-methylmorpholine-N-oxide and then 0.0027 ml of 2% aqueous osmium tetroxide solution were added under cooling with ice, followed by 66 hours' stirring at room temperature. An aqueous sodium thiosulfate solution was added to the reaction liquid, followed by extraction with chloroform and drying over anhydrous sodium sulfate. Distilling the solvent off under reduced pressure, the resulting residue was purified with a preparative thin-layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art 5744 (Merck), chloroform/methanol = 10/1) to provide 21 mg of the title compound.

(Step 4)

Synthesis of (2R)-1-((2S, 3R, 4S)-3,4-dihydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-N-((3S)-3-piperidylmethyl)-pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Step 2 of Example 17, using (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)-1-((2S, 3R, 4S)-3,4-dihydroxy-1-

(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonylpyrrolidine-2-

5 carboxamide. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.80-2.10(12H, m), 2.10-2.25

(2H, m), 2.48-2.60(1H, m), 2.65-2.94(4H, m), 3.45

(1H, d, J=14.8Hz), 3.50-3.68(2H, m), 3.77(1H, d, J=14.8Hz),

3.78-3.84(1H, m), 4.10-4.20(3H, m), 4.51-4.56(1H, m),

10 7.17-7.32(16H, m)

FAB-MS(m/e, as (C<sub>37</sub>H<sub>44</sub>N<sub>4</sub>O<sub>5</sub>+H)<sup>+</sup>): 625

#### Example 83

(2R)-N-(((3R)-1-ethyl-3-piperidyl)methyl)-1-((2S, 3R, 4S)-3,4-  
15 dihydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonyl-  
pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Example 77, using (2R)-1-((2S, 3R, 4S)-3,4-dihydroxy-1-(3,3,3-

triphenylpropanoyl)pyrrolidin-2-yl}carbonyl-N-((3S)-3-piperidyl-

20 methyl)pyrrolidine-2-carboxamide and ethyl iodide. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.77-2.10(15H, m), 2.20-2.28

(1H, m), 2.30-2.42(2H, m), 2.46-2.60(1H, m), 2.73-2.82(1H, m),

2.84-2.93(2H, m), 2.94-3.04(1H, m), 3.42(1H, d, J=14.5Hz),

25 3.50-3.64(2H, m), 3.76-3.83(1H, m), 3.85(1H, d, J=14.5Hz),

4.09-4.17(2H, m), 4.18-4.22(1H, m), 9.06

(1H, dd, J=1.4, 8.2Hz), 7.13-7.30(16H, m)

FAB-MS(m/e, as (C<sub>39</sub>H<sub>48</sub>N<sub>4</sub>O<sub>5</sub>+H)<sup>+</sup>): 653

#### 30 Example 84

(2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-1-  
{{(2S, 3R, 4S)-3,4-dihydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-  
yl}carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Step 3 of Example 17, using (2R)-1-((2S,3R,4S)-3,4-dihydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)-carbonyl-N-((3S)-3-piperidylmethyl)pyrrolidine-2-carboxamide. The compound was  
5 obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.75-0.98(3H, m), 1.12-1.42(5H, m),  
1.43-2.04(15H, m), 2.05(2H, d, J=6.5Hz), 2.18-2.27(1H, m),  
2.28-2.40(1H, m), 2.57-2.63(1H, m), 2.70-2.80(1H, m),  
2.93-3.12(2H, m), 3.44(1H, d, J=14.5Hz), 3.51-3.63(2H, m),  
10 3.76-3.80(1H, m), 3.81(1H, d, J=14.5Hz), 4.12-4.19(2H, m),  
4.20-4.25(1H, m), 4.49-4.54(1H, m), 7.13-7.32(16H, m)  
FAB-MS(m/e, as (C<sub>44</sub>H<sub>56</sub>N<sub>4</sub>O<sub>5</sub>+H)<sup>+</sup>): 721

#### Example 85

15 (2R)-1-((2S, 4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-pyrrolidin-2-yl)carbonyl-N-(((3R)-1-isobutyl-3-piperidyl)methyl)-pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Example 47, using isobutylaldehyde. The compound was obtained as  
20 a colorless oily substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.75-2.10(22H, m), 2.22-2.32  
(1H, m), 2.55-2.85(4H, m), 3.01-3.11(1H, m), 3.30-3.43  
(2H, m), 3.55-3.68(1H, m), 3.80-4.00(2H, m), 4.27-4.38(2H, m),  
4.50-4.59(1H, m), 7.13-7.40(16H, m)  
25 ESI-MS(m/e, as (C<sub>41</sub>H<sub>52</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 665

#### Example 86

(2R)-N-(((3R)-1-propyl-3-piperidyl)methyl)-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-  
30 carboxamide

The title compound was prepared by a method similar to Step 3 of Example 17, using (2R)-N-((3S)-3-piperidylmethyl)-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-



carboxamide and propionaldehyde. The product was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.75-2.10(16H, m), 0.90  
(3H, t, J=7.3Hz), 2.23-2.42(3H, m), 2.69-2.86(2H, m),  
5 2.87-3.07(3H, m), 3.29-3.40 (2H, m), 3.42  
(1H, d, J=14.2Hz), 3.78-3.88(1H, m), 3.98(1H, d, J=14.2Hz),  
4.02-4.10(1H, m), 4.53-4.59(1H, m), 7.15-7.40(16H, m)  
ESI-MS(m/e, as (C<sub>40</sub>H<sub>50</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 635

#### 10 Example 87

(2R)-N-(((3R)-1-butyl-3-piperidyl)methyl)-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
15 Example 85, using n-butylaldehyde. The product was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.80-2.50(21H, m), 0.92  
(3H, t, J=7.3Hz), 2.69-2.83(2H, m), 2.85-3.09(3H, m),  
3.29-3.40(2H, m), 3.41 (1H, d, J=14.6Hz), 3.78-3.86(1H, m),  
20 3.99(1H, d, J=14.6Hz), 4.02-4.08(1H, m), 4.52-4.60(1H, m),  
7.15-7.40(16H, m)  
ESI-MS(m/e, as (C<sub>41</sub>H<sub>52</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 649

#### Example 88

25 (2R)-N-((1-benzyl-2-piperidyl)methyl)-1-((2S)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
Example 63, using 2-aminomethyl-1-benzylpiperidine [cf. Chem.  
30 Pharm. Bull., 43, 1137-1147 (1995)]. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.70-2.08(13H, m), 2.27-2.39  
(1H, m), 2.42-2.59(1H, m), 2.60-2.85(2H, m), 3.80-3.45(6H, m),

3.50-4.18(5H, m), 4.57-4.62(1H, m), 7.10-7.40(21H, m)

ESI-MS(m/e, as (C<sub>44</sub>H<sub>50</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 683

#### Example 89

5        (2R)-1-((2S, 4R)-4-hydroxy-1-{3,3,3-tris(4-chlorophenyl)-propanoyl}pyrrolidin-2-yl)carbonyl-N-(((3S)-3-piperidyl)methyl)-pyrrolidine-2-carboxamide

The title compound was prepared by successively conducting procedures similar to Step 4 of Example 45 and Example 46, using  
10    3,3,3-tris(4-chlorophenyl)propionic acid. The product was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.80-2.10(13H, m), 2.27-2.35  
(1H, m), 2.48-2.59(2H, m), 2.84-3.06(4H, m), 3.34-3.42(1H, m),  
3.36(1H, d, J=15.0Hz), 3.61(1H, dd, J=3.8, 11.0Hz), 3.79  
15    (1H, d, J=15.0Hz), 3.80-3.87(1H, m), 4.37-4.48(2H, m),  
4.55(1H, d, J=6.3Hz), 7.03-7.10(1H, m), 7.14(6H, d, J=8.7Hz),  
7.25(6H, d, J=8.7Hz)

ESI-MS(m/e, as (C<sub>37</sub>H<sub>41</sub>Cl<sub>3</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 711

#### 20    Example 90

(2R)-1-((2S, 4R)-4-hydroxy-1-{3,3,3-tris(4-fluorophenyl)-propanoyl}pyrrolidin-2-yl)carbonyl-N-(((3S)-3-piperidyl)methyl)-pyrrolidine-2-carboxamide

The title compound was prepared by successively conducting  
25    procedures similar to Step 4 of Example 45 and Example 46, using  
3,3,3-tris(4-fluorophenyl)propionic acid. The product was obtained as a pale yellow solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.83-2.07(12H, m), 2.08-2.18  
(1H, m), 2.25-2.34(1H, m), 2.48-2.60(2H, m), 2.88-3.05(4H, m),  
30    3.32-3.40 (1H, m), 3.41(1H, d, J=15.1Hz), 3.58-3.63(1H, m),  
3.77(1H, d, J=15.1Hz), 3.80-3.88(1H, m), 4.37-4.50(2H, m),  
4.51-4.57(1H, m), 6.96(6H, dd, J<sub>HF</sub>=8.6Hz, J<sub>HH</sub>=8.6Hz),  
7.05-7.20(1H, m), 7.17(6H, dd, J<sub>HF</sub>=5.3Hz, J<sub>HH</sub>=8.6Hz)

ESI-MS(m/e, as (C<sub>37</sub>H<sub>41</sub>F<sub>3</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 663

Example 91

(2R)-1-((2S, 4R)-4-hydroxy-1-{3,3,3-tris(4-methylphenyl)-  
5 propanoyl}pyrrolidin-2-yl)carbonyl-N-(((3S)-3-piperidyl)methyl)-  
pyrrolidine-2-carboxamide  
(Step 1)

Synthesis of methyl 3,3,3-tris(4-chlorophenyl)propionate

The title compound was prepared by a method similar to  
10 Step 1 of Example 24, using 3,3,3-tris(4-chlorophenyl)propionic acid.  
(Step 2)

Synthesis of methyl 3,3,3-tris(4-vinylphenyl)propionate

The title compound was synthesized referring to Shirakawa,  
et al.'s method [J. Chem. Soc., Perkin Trans. 1, 2449-2450 (1997)]. To  
15 a solution of 71 mg of nickel (II)-acetylacetonate dihydrate and 289  
mg of triphenylphosphine in 2 ml of 1,2-dimethoxyethane, 0.544 ml of  
1.0 M diisobutylaluminium hydride-toluene solution was added at  
room temperature in nitrogen atmosphere, and the whole system was  
added to a solution of 364 mg of methyl 3,3,3-tris (4-chlorophenyl)-  
20 propionate and 1.01 g of vinyltributyltin in 5 ml of 1,2-dimethoxy-  
ethane at room temperature, followed by 22 hours' stirring at 80°C  
Further, a system formed by adding 0.544 ml of 1.0 M diisobutyl-  
aluminium hydride-toluene solution to a solution of 71 mg of nickel  
(II)-acetylacetonate dihydrate and 289 mg of triphenylphosphine in 2  
25 ml of 1,2-dimethoxyethane at room temperature in nitrogen  
atmosphere was added at room temperature, followed by 17 hours'  
stirring at 80°C under heating. The reaction liquid was cooled to  
room temperature and 1N potassium fluoride was added, followed by  
2 hours' stirring at room temperature. Filtering the reaction liquid  
30 through cerite, the filtrate was diluted with ethyl acetate, washed  
successively with water and saturated brine, and dried over  
anhydrous sodium sulfate. Distilling the solvent off under reduced  
pressure, the resulting residue was purified by means of silica gel

column chromatography (eluting solvent: hexane/ethyl acetate = 300/7 — hexane/ethyl acetate = 300/10) to provide 166 mg of the title compound.

(Step 3)

5                    Synthesis of 3,3,3-tris(4-vinylphenyl)propionic acid

Fifty-four (54) mg of methyl 3,3,3-tris(4-vinylphenyl)-  
pripionate was suspended in 0.5 ml of dioxane, and to the suspension  
0.5 ml of 4N aqueous lithium hydroxide solution was added at room  
temperature, followed by 17 hours' stirring at 90°C under heating.

10    The reaction liquid was made acidic by addition of 1N hydrochloric  
acid, extracted with chloroform and dried over anhydrous sodium  
sulfate. Distilling the solvent off under reduced pressure, 52.5 mg of  
the title compound was obtained.

(Step 4)

15                    Synthesis of (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-  
piperidyl)methyl)-1-((2S,4R)-4-(tert-butoxy)-1-{3,3,3-tris(4-vinyl-  
phenyl)propanoyl}pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
Step 4 of Example 45, using 3,3,3-tris(4-vinylphenyl)propionic acid.

20    (Step 5)

Synthesis of (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-  
piperidyl)methyl)-1-((2S,4R)-4-(tert-butoxy)-1-{3,3,3-tris(4-  
hydroxymethylphenyl)propanoyl}pyrrolidin-2-yl)carbonylpyrrolidine-  
2-carboxamide

25                    To a solution of 30.6 mg of (2R)-N-(((3R)-1-(tert-butoxy-  
carbonyl)-3-piperidyl)methyl)-1-((2S,4R)-4-(tert-butoxy)-1-{3,3,3-  
tris(4-vinylphenyl)propanoyl}pyrrolidin-2-yl)carbonylpyrrolidine-2-  
carboxamide and 48 mg of sodium periodate in 3 ml of 50% hydrous  
acetonitrile, 0.023 ml of 2% aqueous osmium tetroxide solution was  
30    added at room temperature in nitrogen atmosphere, followed by 20  
hours' stirring at the same temperature. To the reaction liquid 41

mg of sodium borohydride was added under cooling with ice, followed by 4 hours' stirring at room temperature. To the reaction liquid an aqueous sodium thiosulfate solution was added, followed by filtration with cerite, extraction with chloroform, and drying over anhydrous sodium sulfate. Distilling the solvent off under reduced pressure, the resulting residue was purified by preparative thin layer chromatography [Kieselgel™ 60F<sub>254</sub>, Art 5744 (Merck); chloroform / methanol = 10/1], to provide 8.4 mg of the title compound.

(Step 6)

10            Synthesis of (2R)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-methylphenyl)propanoyl}pyrrolidin-2-yl)carbonyl-N-(((3S)-3-piperidyl)methyl)pyrrolidine-2-carboxamide

              The title compound was prepared by successively conducting procedures similar to Example 79, Step 2 of Example 45 and Example 15 46, using (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)-1-((2S,4R)-4-(tert-butoxy)-1-{3,3,3-tris(4-hydroxymethylphenyl)propanoyl}pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide. The product was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.82-2.29(14H, m), 2.30(9H,s),  
20            2.50-2.67(2H, m), 2.92(2H, t, J=6.2Hz), 2.98-3.10(2H, m),  
              3.32-3.41(1H, m), 3.33(1H, d, J=14.1Hz), 3.58-3.68(1H, m),  
              3.86(1H, d, J=14.1Hz), 3.87-3.91(1H, m), 4.25-4.36(2H, m),  
              4.50-4.58(1H, m), 7.06(6H, d, J=8.3Hz), 7.18(6H, d, J=8.3Hz),  
              7.37-7.46(1H, m)

25            ESI-MS(m/e, as (C<sub>40</sub>H<sub>50</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 651

#### Example 92

(2R)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-ethylphenyl)-  
propanoyl}pyrrolidin-2-yl)carbonyl-N-(((3S)-3-piperidyl)methyl)-  
30            pyrrolidine-2-carboxamide

(Step 1)

Synthesis of (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)-1-((2S,4R)-4-(tert-butoxy)-1-{3,3,3-tris(4-ethylphenyl)propanoyl}pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

To a solution of 15.6 mg of (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)-1-((2S,4R)-4-(tert-butoxy)-1-{3,3,3-tris(4-vinylphenyl)propanoyl}pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide in 0.6 ml of methanol, 5 mg of 10% palladium-carbon catalyst was added at room temperature, followed by 4.5 hours' stirring in hydrogen atmosphere. After filtering the catalyst off, the solvent was distilled off under reduced pressure to provide 12 mg of the title compound.

(Step 2)

Synthesis of (2R)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-ethylphenyl)propanoyl}pyrrolidin-2-yl)carbonyl-N-(((3S)-3-piperidyl)methyl)pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Example 46, using (2R)-N-(((3R)-1-(tert-butoxycarbonyl)-3-piperidyl)methyl)-1-((2S,4R)-4-(tert-butoxy)-1-{3,3,3-tris(4-ethylphenyl)propanoyl}pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide. The compound was obtained as a white solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.97\text{-}2.10(12\text{H}, \text{m}), 1.22(9\text{H}, \text{t}, J=7.6\text{Hz}), 2.12\text{-}2.35(2\text{H}, \text{m}), 2.48\text{-}2.60(2\text{H}, \text{m}), 2.62(6\text{H}, \text{q}, J=7.6\text{Hz}), 2.78\text{-}3.03(4\text{H}, \text{m}), 3.30\text{-}3.40(1\text{H}, \text{m}), 3.34(1\text{H}, \text{d}, J=14.0\text{Hz}), 3.58\text{-}3.65(1\text{H}, \text{m}), 3.80\text{-}3.86(1\text{H}, \text{m}), 3.87(1\text{H}, \text{d}, J=14.0\text{Hz}), 4.27\text{-}4.38(2\text{H}, \text{m}), 4.52\text{-}4.59(1\text{H}, \text{m}), 7.08(6\text{H}, \text{d}, J=8.3\text{Hz}), 7.20(6\text{H}, \text{d}, J=8.3\text{Hz}), 7.27\text{-}7.40(1\text{H}, \text{m})$   
ESI-MS(m/e, as  $(\text{C}_{43}\text{H}_{56}\text{N}_4\text{O}_4+\text{H})^+$ ): 693

Example 93

(2R)-N-(((3R)-1-ethyl-3-piperidyl)methyl)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-ethylphenyl)propanoyl}pyrrolidin-2-yl)-carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
5 Example 77, using (2R)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-ethylphenyl)propanoyl}pyrrolidin-2-yl)carbonyl-N-(((3S)-3-piperidyl)-methyl)pyrrolidine-2-carboxamide and ethyl iodide. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.78-1.15(6H, m), 1.22  
10 (9H, t, J=7.6Hz), 1.28-2.10(11H, m), 2.24-2.32(1H, m),  
2.32-2.48(2H, m), 2.61(6H, q, J=7.6Hz), 2.75-3.04  
(4H, m), 3.29-3.40(2H, m), 3.60-3.68(1H, m), 3.83-4.01  
(2H, m), 4.20-4.33(2H, m), 4.50-4.59(1H, m), 7.08  
(6H, d, J=8.4Hz), 7.23(6H, d, J=8.4Hz), 7.30-7.42(1H, m)  
15 ESI-MS(m/e, as (C<sub>45</sub>H<sub>60</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 721

#### Example 94

(2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-pyrrolidin-2-yl)carbonyl-N-((3R)-3-piperidylmethyl)pyrrolidine-2-  
20 carboxamide

The title compound was prepared by successively conducting procedures similar to Steps 1-4 of Example 45 and Example 46, using (3S)-3-aminomethyl-1-(tert-butoxycarbonyl)piperidine. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.88-2.08(12H, m), 2.21  
25 (1H, t, J=11.0Hz), 2.27-2.36(1H, m), 2.46-2.58(2H, m),  
2.78-2.99(3H, m), 3.00-3.12(1H, m), 3.30-3.40(1H, m), 3.44  
(1H, d, J=14.7Hz), 3.62(1H, dd, J=4.0, 10.9Hz), 3.78-3.85  
(1H, m), 3.86(1H, d, J=14.7Hz), 4.30-4.40(2H, m),  
30 4.55-4.62(1H, m), 7.15-7.38(16H, m)

ESI-MS(m/e, as (C<sub>37</sub>H<sub>44</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 609

Example 95

(2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-  
5 pyrrolidin-2-yl)carbonyl-N-(((3S)-1-methyl-3-piperidyl)methyl)-  
pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
Step 3 of Example 17, using (2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-  
triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-N-((3R)-3-piperidyl-  
10 methyl)pyrrolidine-2-carboxamide and 37% aqueous formaldehyde  
solution. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.68-2.10(13H, m), 2.24(3H, s),  
2.25-2.33(1H, m), 2.46-2.55(1H, m), 2.57-2.68(1H, m),  
2.73-2.86(2H, m), 3.03-3.14(1H, m), 3.29-3.40(1H, m),  
15 3.42(1H, d, J=14.8Hz), 3.61(1H, dd, J=4.0, 10.7Hz),  
3.79-3.86(1H, m), 3.87(1H, d, J=14.8Hz), 4.32-4.40(2H, m),  
4.54-4.60(1H, m), 7.15-7.35(16H, m)

ESI-MS(m/e, as (C<sub>38</sub>H<sub>46</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 623

20 Example 96

(2R)-N-(((3S)-1-ethyl-3-piperidyl)methyl)-1-((2S,4R)-4-  
hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)-  
carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
25 Example 95, using acetaldehyde. The product was obtained as a  
white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.78-2.32(14H, m), 1.06  
(3H, t, J=7.2Hz), 2.33-2.47(3H, m), 2.71-2.79(1H, m),  
2.82-2.92(2H, m), 3.00-3.12(1H, m), 3.29-3.38(1H, m),  
30 3.44(1H, d, J=14.8Hz), 3.59(1H, dd, J=4.0, 10.9Hz),



3.79-3.85(1H, m), 3.86(1H, d, J=14.8Hz), 4.32-4.40(2H, m),  
4.55(1H, d, J=6.6Hz), 7.13-7.32(16H, m)

ESI-MS(m/e, as (C<sub>39</sub>H<sub>48</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 637

5 Example 97

(2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-  
pyrrolidin-2-yl)carbonyl-N-(((3S)-1-propyl-3-piperidyl)methyl)-  
pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
10 Example 95, using propionaldehyde. The product was obtained as a  
white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.69-2.08(15H, m), 0.87  
(3H, t, J=7.4Hz), 2.08-2.38(3H, m), 2.49-2.60(1H, m),  
2.72-2.93(3H, m), 3.00-3.13(1H, m), 3.29-3.40(1H, m), 3.41  
15 (1H, d, J=14.6Hz), 3.60(1H, dd, J=3.8, 11.0Hz), 3.80-3.87  
(1H, m), 3.87(1H, d, J=14.6Hz), 4.30-4.44(2H, m), 4.55-4.62  
(1H, m), 7.15-7.43(16H, m)

ESI-MS(m/e, as (C<sub>40</sub>H<sub>50</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 651

20 Example 98

(2R)-N-(((3S)-1-cyclopropylmethyl-3-piperidyl)methyl)-1-((2S,  
4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)-  
carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
25 Example 95, using cyclopropanecarbaldehyde. The product was  
obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.05-0.18(2H, m), 0.43-0.55(2H, m),  
0.70-2.07(14H, m), 2.18-2.34(3H, m), 2.42-2.55(1H, m),  
2.78-2.94(2H, m), 2.97-3.15(2H, m), 3.30-3.41(1H, m),  
30 3.43(1H, d, J=14.9Hz), 3.60(1H, dd, J=4.0, 11.1Hz),

3.78-3.86(1H, m), 3.89(1H, d, J=14.9Hz), 4.30-4.40(2H, m),  
4.57(1H, d, J=7.3Hz), 7.12-7.30(16H, m)  
ESI-MS(m/e, as (C<sub>41</sub>H<sub>50</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 663

5    Example 99

(2R)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-chlorophenyl)-  
propanoyl}pyrrolidin-2-yl)carbonyl-N-(((3R)-3-piperidyl)methyl)-  
pyrrolidine-2-carboxamide

(Step 1)

10            Synthesis of (2R)-N-(((3S)-1-(tert-butoxycarbonyl)-3-  
piperidyl)methyl)-1-((2S,4R)-4-(tert-butoxy)pyrrolidin-2-yl)-  
carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
Steps 1-3 of Example 45, using (3S)-3-aminomethyl-1-(tert-  
15    butoxycarbonyl)piperidine.

(Step 2)

Synthesis of (2R)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-  
chlorophenyl)propanoyl}pyrrolidin-2-yl)carbonyl-N-(((3R)-3-  
piperidyl)methyl)pyrrolidine-2-carboxamide

20            The title compound was prepared by a method similar to  
Example 88, using (2R)-N-(((3S)-1-(tert-butoxycarbonyl)-3-  
piperidyl)methyl)-1-((2S,4R)-4-(tert-butoxy)pyrrolidin-2-yl)-  
carbonylpyrrolidine-2-carboxamide. The product was obtained as a  
white foamy substance.

25            <sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.83-1.82(8H, m), 1.88-2.10(4H, m),  
2.13-2.22(1H, m), 2.28-2.40(2H, m), 2.48-2.59(1H, m),  
2.80-2.88(1H, m), 2.90-3.07(2H, m), 3.08-3.20(1H, m),  
3.29-3.39(1H, m), 3.39(1H, d, J=15.3Hz), 3.60-3.66(1H, m),  
3.73(1H, d, J=15.3Hz), 3.77-3.86(1H, m), 4.39-4.52(2H, m),

4.57(1H, d, J=5.6Hz), 7.02-7.20(1H, m), 7.12(6H, d, J=8.9Hz),  
7.24(6H, d, J=8.9Hz)

ESI-MS(m/e, as (C<sub>37</sub>H<sub>41</sub>Cl<sub>3</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 711

5 Example 100

(2R)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-fluorophenyl)-  
propanoyl}pyrrolidin-2-yl)carbonyl-N-(((3R)-3-piperidyl)methyl)-  
pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
10 Step 2 of Example 99, using 3,3,3-tris(4-fluorophenyl)propionic acid.  
The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.85-2.10(12H, m), 2.12-2.23  
(1H, m), 2.25-2.40(2H, m), 2.47-2.58(1H, m), 2.80-2.90(1H, m),  
2.91-3.00(1H, m), 3.04-3.18(2H, m), 3.30-3.42(1H, m),  
15 3.45(1H, d, J=15.4Hz), 3.62(1H, dd, J=4.3, 10.9Hz), 3.72  
(1H, d, J=15.4Hz), 3.77-3.85(1H, m), 4.40-4.50(2H, m),  
4.52-4.60(1H, m), 6.96(6H, dd, J<sub>HF</sub>=8.9Hz, J<sub>HH</sub>=8.9Hz),  
7.09-7.20(1H, m), 7.15(6H, dd, J<sub>HF</sub>=5.3Hz, J<sub>HH</sub>=8.9Hz)

ESI-MS(m/e, as (C<sub>37</sub>H<sub>41</sub>F<sub>3</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 663

20

Example 101

(2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-  
pyrrolidin-2-yl)carbonyl-N-(4-piperidylmethyl)pyrrolidine-2-  
carboxamide

25 (Step 1)

Synthesis of methyl (2R)-1-((2S,4R)-4-(tert-butoxy)-  
pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxylate

The title compound was prepared by procedures similar to  
Steps 1-2 of Example 45, using methyl (2R)-pyrrolidine-2-carboxylate  
30 and N-α-benzyloxycarbonyl-O-(tert-butyl)-trans-4-hydroxy-L-proline.

(Step 2)

Synthesis of (2R)-1-((2S,4R)-4-(tert-butoxy)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxylic acid

5           The title compound was obtained by successively conducting procedures which were similar to Step 4 of Example 45 and Step 4 of Example 1, using methyl (2R)-1-((2S,4R)-4-(tert-butoxy)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxylate.

(Step 3)

10           Synthesis of (2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-N-(4-piperidylmethyl)pyrrolidine-2-carboxamide

          The title compound was prepared by successively conducting procedures which were similar to Step 5 of Example 1 and Example  
15 46, using (2R)-1-((2S,4R)-4-(tert-butoxy)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxylic acid and 4-aminomethyl-1-(tert-butoxycarbonyl)piperidine. The compound was obtained as a colorless oily substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 1.18-1.72(6H, m), 1.75-2.09(5H, m),  
20 2.19-2.30(1H, m), 2.57-2.76(3H, m), 2.86(1H, d, J=10.6Hz),  
3.00-3.12(1H, m), 3.18-3.40(3H, m), 3.52(1H, d, J=14.8Hz),  
3.57(1H, dd, J=4.0, 11.0Hz), 3.78(1H, d, J=14.8Hz),  
3.79-3.86(2H, m), 4.30-4.40(2H, m), 4.50-4.59(1H, m),  
7.13-7.32(15H, m), 7.33-7.41(1H, m)

25           ESI-MS(m/e, as (C<sub>37</sub>H<sub>44</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 609

Example 102

(2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-tris(4-chlorophenyl)propanoyl)pyrrolidin-2-yl)carbonyl-N-(4-piperidylmethyl)pyrrolidine-

## 2-carboxamide

The title compound was prepared by procedures similar to Steps 2-3 of Example 101, using 3,3,3-tris(4-chlorophenyl)propionic acid. The compound was obtained as a white foamy substance.

5  $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.83\text{-}2.08(12\text{H}, \text{m}), 2.29\text{-}2.45$   
(2H, m), 2.46-2.58(2H, m), 2.98-3.16(4H, m), 3.30-3.38(1H, m),  
3.39(1H, d,  $J=15.0\text{Hz}$ ), 3.63(1H, dd,  $J=4.1, 10.8\text{Hz}$ ), 3.71  
(1H, d,  $J=15.0\text{Hz}$ ), 3.76-3.86(1H, m), 4.38-4.51(2H, m),  
4.58(1H, d,  $J=5.9\text{Hz}$ ), 7.05-7.20(1H, m), 7.12(6H, d,  $J=8.8\text{Hz}$ ),  
10 7.24(6H, d,  $J=8.8\text{Hz}$ )  
ESI-MS( $m/e$ , as  $(\text{C}_{37}\text{H}_{41}\text{Cl}_3\text{N}_4\text{O}_4+\text{H})^+$ ): 711

## Example 103

(2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-tris(4-fluorophenyl)-  
15 propanoyl)pyrrolidin-2-yl)carbonyl-N-(4-piperidylmethyl)pyrrolidine-  
2-carboxamide

The title compound was prepared by procedures similar to Steps 2-3 of Example 101, using 3,3,3-tris(4-fluorophenyl)propionic acid. The compound was obtained as a white solid.

20  $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.80\text{-}2.08(12\text{H}, \text{m}), 2.28\text{-}2.45$   
(2H, m), 2.46-2.57(2H, m), 2.98-3.12(4H, m), 3.32-3.40(1H, m),  
3.44(1H, d,  $J=15.1\text{Hz}$ ), 3.59(1H, dd,  $J=4.1, 10.8\text{Hz}$ ), 3.69  
(1H, d,  $J=15.1\text{Hz}$ ), 3.77-3.87(1H, m), 4.40-4.51(2H, m),  
4.53-4.61(1H, m), 6.96(6H, dd,  $J_{\text{HF}}=8.8\text{Hz}, J_{\text{HH}}=8.8\text{Hz}$ ),  
25 7.08-7.20(1H, m), 7.15(6H, dd,  $J_{\text{HF}}=5.2\text{Hz}, J_{\text{HH}}=8.8\text{Hz}$ )  
ESI-MS( $m/e$ , as  $(\text{C}_{37}\text{H}_{41}\text{F}_3\text{N}_4\text{O}_4+\text{H})^+$ ): 663

## Example 104

(2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-  
30 pyrrolidin-2-yl)carbonyl-N-(4-piperidylethyl)pyrrolidine-2-

carboxamide

The title compound was prepared by a method similar to Step 3 of Example 101 using 4-aminoethyl-1-(tert-butoxycarbonyl)-piperidine. The compound was obtained as a pale yellow oily substance.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 1.02\text{-}2.40(15\text{H}, \text{m}), 2.52\text{-}2.64(2\text{H}, \text{m}), 2.65\text{-}2.78(1\text{H}, \text{m}), 2.85(1\text{H}, \text{d}, \text{H}=10.8\text{Hz}), 3.02\text{-}3.11(2\text{H}, \text{m}), 3.12\text{-}3.24(1\text{H}, \text{m}), 3.29\text{-}3.40(1\text{H}, \text{m}), 3.45(1\text{H}, \text{d}, \text{J}=14.6\text{Hz}), 3.58(1\text{H}, \text{dd}, \text{J}=4.0, 10.9\text{Hz}), 3.78\text{-}3.82(1\text{H}, \text{m}), 3.83(1\text{H}, \text{d}, \text{J}=14.6\text{Hz}), 4.32\text{-}4.40(2\text{H}, \text{m}), 4.52\text{-}4.59(1\text{H}, \text{m}), 7.12\text{-}7.31(16\text{H}, \text{m})$

ESI-MS( $m/e$ , as  $(\text{C}_{38}\text{H}_{46}\text{N}_4\text{O}_4+\text{H})^+$ ): 623

Example 105

(2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-pyrrolidin-2-yl)carbonyl-N-(1-methyl-4-piperidylethyl)pyrrolidine-2-carboxamide

The title compound was obtained by a method similar to Step 3 of Example 17, using (2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidine-2-yl)carbonyl-N-(4-piperidylethyl)pyrrolidine-2-carboxamide and 37% aqueous formaldehyde solution. The compound was obtained as a colorless oily substance.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 1.05\text{-}2.08(15\text{H}, \text{m}), 2.28(3\text{H}, \text{s}), 2.29\text{-}2.36(1\text{H}, \text{m}), 2.70\text{-}2.92(4\text{H}, \text{m}), 3.12\text{-}3.28(1\text{H}, \text{m}), 3.30\text{-}3.42(1\text{H}, \text{m}), 3.43(1\text{H}, \text{d}, \text{J}=14.5\text{Hz}), 3.59(1\text{H}, \text{dd}, \text{J}=3.8, 10.9\text{Hz}), 3.78\text{-}3.83(1\text{H}, \text{m}), 3.84(1\text{H}, \text{d}, \text{J}=14.5\text{Hz}), 4.32\text{-}4.41(2\text{H}, \text{m}), 4.53\text{-}4.60(1\text{H}, \text{m}), 7.13\text{-}7.33(16\text{H}, \text{m})$

ESI-MS( $m/e$ , as  $(\text{C}_{39}\text{H}_{48}\text{N}_4\text{O}_4+\text{H})^+$ ): 637

Example 106

(2R)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-chlorophenyl)-propanoyl}pyrrolidin-2-yl)carbonyl-N-(4-piperidylethyl)pyrrolidine-2-carboxamide

5           The title compound was prepared by successively conducting procedures similar to Step 2 of Example 101 and Example 104, using 3,3,3-tris(4-chlorophenyl)propionic acid. The compound was obtained as a white foamy substance.

10           <sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.95-1.88(10H, m), 1.90-2.00 (2H, m), 2.01-2.12(2H, m), 2.28-2.38(1H, m), 2.46-2.60(3H, m), 2.98-3.11(3H, m), 3.20-3.38(2H, m), 3.40(1H, d, J=15.4Hz), 3.63(1H, dd, J=4.1, 11.0Hz), 3.71(1H, d, J=15.4Hz), 3.73-3.82(1H, m), 4.39-4.52(2H, m), 4.53-4.60(1H, m), 6.98-7.05(1H, m), 7.10(6H, d, J=8.8Hz), 7.23(6H, d, J=8.8Hz)  
15           ESI-MS(m/e, as (C<sub>38</sub>H<sub>43</sub>Cl<sub>3</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 725

Example 107

(2R)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-fluorophenyl)-propanoyl}pyrrolidin-2-yl)carbonyl-N-(4-piperidylethyl)pyrrolidine-2-carboxamide

20           The title compound was prepared by successively conducting procedures similar to Step 2 of Example 101 and Example 104, using 3,3,3-tris(4-fluorophenyl)propionic acid. The compound was obtained as a white solid.

25           <sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.85-1.86(10H, m), 1.88-2.00 (2H, m), 2.00-2.10(2H, m), 2.27-2.36(1H, m), 2.47-2.60(3H, m), 2.98-3.06(2H, m), 3.07-3.14(1H, m), 3.15-3.28(1H, m), 3.30-3.41(1H, m), 3.45(1H, d, J=15.5Hz), 3.60 (1H, dd, J=4.2, 10.6Hz), 3.70(1H, d, J=15.5Hz), 3.75-3.85  
30           (1H, m), 4.41-4.52(2H, m), 4.53-4.60(1H, m), 6.94

(6H, dd,  $J_{\text{HF}}=8.5\text{Hz}$ ,  $J_{\text{HH}}=8.5\text{Hz}$ ), 7.00-7.10(1H, m), 7.13

(6H, dd,  $J_{\text{HF}}=5.3\text{Hz}$ ,  $J_{\text{HH}}=8.5\text{Hz}$ )

ESI-MS( $m/e$ , as  $(\text{C}_{38}\text{H}_{43}\text{F}_3\text{N}_4\text{O}_4+\text{H})^+$ ): 677

5 Example 108

(2R)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-fluorophenyl)-  
propanoyl}pyrrolidin-2-yl)carbonyl-N-(1-methyl-4-piperidylmethyl)-  
pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
10 Example 105, using (2R)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-fluoro-  
phenyl)propanoyl}pyrrolidin-2-yl)carbonyl-N-(4-piperidylmethyl)-  
pyrrolidine-2-carboxamide. The compound was obtained as a white  
solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm})$ : 1.12-2.20(13H, m), 2.31(3H, s),  
15 2.32-2.39(1H, m), 2.48-2.58(1H, m), 2.83-2.94(2H, m),  
2.99-3.10(2H, m), 3.35-3.42(1H, m), 3.45(1H, d,  $J=15.0\text{Hz}$ ),  
3.62(1H, dd,  $J=4.1, 11.0\text{Hz}$ ), 3.73(1H, d,  $J=15.0\text{Hz}$ ),  
3.78-3.88(1H, m), 4.40-4.53(2H, m), 4.59(1H, d,  $J=5.9\text{Hz}$ ),  
6.92-7.03(6H, m), 7.08-7.25(7H, m)

20 ESI-MS( $m/e$ , as  $(\text{C}_{38}\text{H}_{43}\text{F}_3\text{N}_4\text{O}_4+\text{H})^+$ ): 677

Example 109

(2R)-N-{(1-ethyl-4-piperidyl)methyl}-1-((2S,4R)-4-hydroxy-1-  
{3,3,3-tris(4-fluorophenyl)propanoyl}pyrrolidin-2-yl)carbonyl-  
25 pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
Exampel 93, using (2R)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-  
fluorophenyl)propanoyl}pyrrolidin-2-yl)carbonyl-N-(4-piperidyl-  
methyl)pyrrolidine-2-carboxamide. The compound was obtained as a



white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 1.03-2.15(16H, m), 2.29-2.48  
(3H, m), 2.50-2.60(1H, m), 2.86-2.96(2H, m), 2.97-3.10(2H, m),  
5 3.30-3.40(1H, m), 3.42(1H, d, J=15.1Hz), 3.63  
(1H, dd, J=3.9, 11.0Hz), 3.72(1H, d, J=15.1Hz), 3.78-3.88  
(1H, m), 4.40-4.52(2H, m), 4.53-4.61(1H, m), 6.96  
(6H, dd, J<sub>HF</sub>=8.8Hz, J<sub>HH</sub>=8.8Hz), 7.07-7.20(1H, m),  
7.16(6H, dd, J<sub>HF</sub>=5.3Hz, J<sub>HH</sub>=8.8Hz)  
10 ESI-MS(m/e, as (C<sub>39</sub>H<sub>45</sub>F<sub>3</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 691

#### Example 110

(2R)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-fluorophenyl)-  
propanoyl}pyrrolidin-2-yl)carbonyl-N-{1-(2-propyl)-4-piperidyl-  
15 methyl}pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
Example 109, using 2-propyl bromide. The compound was obtained  
as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.82-2.17(13H, m), 1.06  
20 (6H, d, J=6.2Hz), 2.28-2.37(1H, m), 2.48-2.59(1H, m),  
2.66-2.93(3H, m), 2.96-3.10(2H, m), 3.32-3.41(1H, m),  
3.43(1H, d, J=15.0Hz), 3.63(1H, dd, J=4.3, 10.8Hz), 3.73  
(1H, d, J=15.0Hz), 3.78-3.88(1H, m), 4.38-4.51(2H, m),  
4.57(1H, d, J=6.7Hz), 6.96(6H, dd, J<sub>HF</sub>=8.8Hz, J<sub>HH</sub>=8.8Hz),  
25 7.08-7.20(1H, m), 7.16(6H, dd, J<sub>HF</sub>=5.4Hz, J<sub>HH</sub>=8.8Hz)  
ESI-MS(m/e, as (C<sub>40</sub>H<sub>47</sub>F<sub>3</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 705

#### Example 111

(2R)-N-{(1-cyclobutylmethyl-4-piperidyl)methyl}-1-((2S,4R)-  
30 4-hydroxy-1-{3,3,3-tris(4-fluorophenyl)propanoyl}pyrrolidin-2-yl)-

carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Example 109, using (bromomethyl)cyclobutane. The compound was obtained as a white solid.

5  $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.82\text{-}2.10(20\text{H}, \text{m}), 2.28\text{-}2.44$   
(2H, m), 2.45-2.60(2H, m), 2.76-2.92(2H, m), 2.97-3.08(2H, m),  
3.30-3.40(1H, m), 3.41(1H, d,  $J=15.1\text{Hz}$ ), 3.57-3.67(1H, m),  
3.72(1H, d,  $J=15.1\text{Hz}$ ), 3.78-3.87(1H, m), 4.39-4.52(2H, m),  
4.54-3.61(1H, m), 6.96(6H, dd,  $J_{\text{HF}}=8.8\text{Hz}$ ,  $J_{\text{HH}}=8.8\text{Hz}$ ),  
10 7.06-7.20(1H, m), 7.15(6H, dd,  $J_{\text{HF}}=5.3\text{Hz}$ ,  $J_{\text{HH}}=8.8\text{Hz}$ )  
ESI-MS( $m/e$ , as  $(\text{C}_{42}\text{H}_{49}\text{F}_3\text{N}_4\text{O}_4+\text{H})^+$ ): 731

Example 112

(2R)-N-{(1-cyclopentylmethyl-4-piperidyl)methyl}-1-((2S,4R)-  
15 4-hydroxy-1-{3,3,3-tris(4-fluorophenyl)propanoyl}pyrrolidin-2-yl)-  
carbonylpyrrolidine-2-carboxamide

To a solution of 19 mg of (2R)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-fluorophenyl)propanoyl}pyrrolidin-2-yl)carbonyl-N-(4-piperidyl-methyl)pyrrolidine-2-carboxamide in 1.5 ml of acetonitrile, 14 mg of  
20 methanesulfonic acid-cyclopentylmethyl, 13 mg of potassium carbonate and 5 mg of potassium iodide were added at room temperature, followed by 24 hours' stirring at 80°C under heating. The reaction liquid was diluted with chloroform, washed successively with water and 1N aqueous sodium hydroxide solution, and dried  
25 over anhydrous sodium sulfate. Distilling the solvent off under reduced pressure, the resultant residue was purified by preparative thin-layer chromatography [Kieselgel™ 60F<sub>254</sub>, Art 5744 (Merck), chloroform/methanol/28% aqueous ammonia = 100/10/1) to provide 16 mg of the title compound as a white solid.

30  $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 1.07\text{-}2.50(26\text{H}, \text{m}), 2.82\text{-}2.98$

(2H, m), 3.00-3.12(2H, m), 3.32-3.40(1H, m), 3.44  
(1H, d, J=15.2Hz), 3.62(1H, dd, J=4.3, 10.8Hz), 3.72  
(1H, d, J=15.2Hz), 3.78-3.88(1H, m), 4.40-4.52(2H, m),  
4.53-4.61(1H, m), 6.96(6H, dd, J<sub>HF</sub>=8.8Hz, J<sub>HH</sub>=8.8Hz),  
5 7.07-7.22(1H, m), 7.15(6H, dd, J<sub>HF</sub>=5.2Hz, J<sub>HH</sub>=8.8Hz)  
ESI-MS(m/e, as (C<sub>43</sub>H<sub>51</sub>F<sub>3</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 745

#### Example 113

(2R)-N-((1-cyclopentyl-4-piperidyl)methyl)-1-((2S,4R)-4-  
10 hydroxy-1-(3,3,3-tris(4-fluorophenyl)propanoyl)pyrrolidin-2-yl)-  
carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
Example 109, using bromocyclopentyl. The compound was obtained  
as a white solid.

15 <sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 1.08-2.20(21H, m), 2.29-2.65  
(3H, m), 3.02-3.18(4H, m), 3.30-3.92(3H, m), 3.42  
(1H, d, J=15.2Hz), 3.71(1H, d, J=15.2Hz), 4.39-4.67(3H, m),  
6.90-7.27(13H, m)  
ESI-MS(m/e, as (C<sub>42</sub>H<sub>49</sub>F<sub>3</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 731

20

#### Example 114

(2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-  
pyrrolidin-2-yl)carbonyl-N-(1-methyl-4-piperidylmethyl)pyrrolidine-  
2-carboxamide

25 The title compound was prepared by a method similar to  
Example 105, using (2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-  
propanoyl)pyrrolidin-2-yl)carbonyl-N-(4-piperidylmethyl)pyrrolidine-  
2-carboxamide. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 1.16-2.08(13H, m), 2.27(3H, s),  
30 2.28-2.36(1H, m), 2.70-2.79(2H, m), 2.80-2.91(2H, m),

2.93-3.04(1H, m), 3.30-3.40(1H, m), 3.43(1H, d, J=14.6Hz),  
3.60(1H, dd, J=3.8, 11.0Hz), 3.85(1H, d, J=14.6Hz),  
3.86-4.01(1H, m), 4.32-4.40(2H, m), 4.58(1H, d, J=6.7Hz),  
7.17-7.36(16H, m)

5 ESI-MS(m/e, as (C<sub>38</sub>H<sub>46</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 623

#### Example 115

(2R)-N-((3S)-1-(1-cyclobutylmethyl-3-piperidyl)methyl)-1-  
((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)-  
10 carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
Example 111, using (2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-  
propanoyl)pyrrolidin-2-yl)carbonyl-N-((3R)-3-piperidylmethyl)-  
pyrrolidine-2-carboxamide. The compound was obtained as a white  
15 solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.65-2.08(19H, m), 2.25-2.33  
(1H, m), 2.35(2H, d, J=6.9Hz), 2.43-2.58(2H, m), 2.60-2.70  
(1H, m), 2.71-2.82(2H, m), 3.00-3.11(1H, m), 3.29-3.39(1H, m),  
3.40(1H, d, J=14.5Hz), 3.59(1H, dd, J=3.8, 11.0Hz),  
20 3.80-3.90(1H, m), 3.87(1H, d, J=14.5Hz), 4.30-4.38(2H, m),  
4.52-4.59(1H, m), 7.14-7.36(16H, m)

ESI-MS(m/e, as (C<sub>42</sub>H<sub>52</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 677

#### Example 116

25 (2R)-N-((3S)-1-(2,2-dimethylcyclopentylmethyl)-3-piperidyl)-  
methyl)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-  
pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
Example 95, using 2,2-dimethylcyclopentanecarbaldehyde which was  
30 synthesized following K.D. Hutchinson, et al. [Tetrahedron, Vol. 50,

6129-6136 (1994)]. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.74(3H, s), 0.80-2.02(20H, m),  
1.01(3H, s), 2.07-2.20(1H, m), 2.21-2.36(2H, m), 2.50-2.92  
(4H, m), 3.00-3.14(1H, m), 3.30-3.40(1H, m), 3.42  
5 (1H, d, J=14.4Hz), 3.61(1H, dd, J=2.4, 11.1Hz), 3.81-3.90  
(1H, m), 3.88(1H, d, J=14.4Hz), 4.30-4.40(2H, m),  
4.55-4.61(1H, m), 7.15-7.38(16H, m)  
ESI-MS(m/e, as (C<sub>45</sub>H<sub>58</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 719

10 Example 117

(2R)-N-(((3S)-1-(2-(1-methylcyclopropyl)ethyl)-3-piperidyl)-  
methyl)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-  
2-yl)carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
15 Examples 95, using 3-cyclopropanebutanal. The compound was  
obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.18-0.30(4H, m), 0.70-2.07  
(15H, m), 1.01(3H, s), 2.24-2.34(1H, m), 2.35-2.57(3H, m),  
2.68-2.92(3H, m), 3.01-3.13(1H, m), 3.29-3.40(1H, m),  
20 3.41(1H, d, J=14.5Hz), 3.60(1H, dd, J=3.8, 11.0Hz),  
3.79-3.87(1H, m), 3.88(1H, d, J=14.5Hz), 4.30-4.39(2H, m),  
4.56-4.61(1H, m), 7.15-7.38(16H, m)  
ESI-MS(m/e, as (C<sub>43</sub>H<sub>54</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 691

25 Example 118

(2R)-N-(((3S)-1-(1-cyclopentylethyl)-3-piperidyl)-  
methyl)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-  
2-yl)carbonylpyrrolidine-2-carboxamide

The title compound was prepared by a method similar to  
30 Example 112, using 1-(cyclopentyl)ethyl 4-methylbenzenesulfonate.

The compound was obtained as a white foamy substance.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.80\text{-}2.08(24\text{H}, \text{m}), 2.15\text{-}2.40$   
 $(3\text{H}, \text{m}), 2.50\text{-}3.15(5\text{H}, \text{m}), 3.30\text{-}3.53(2\text{H}, \text{m}), 3.56\text{-}3.72$   
 $(1\text{H}, \text{m}), 3.78\text{-}3.93(2\text{H}, \text{m}), 4.26\text{-}4.42(2\text{H}, \text{m}), 4.53\text{-}4.62$   
 $(1\text{H}, \text{m}), 7.15\text{-}7.43(16\text{H}, \text{m})$

ESI-MS( $m/e$ , as  $(\text{C}_{44}\text{H}_{56}\text{N}_4\text{O}_4+\text{H})^+$ ): 705

#### Example 119

$(2\text{R})\text{-N-}\{((3\text{S})\text{-}1\text{-}(1\text{-cyclohexylethyl})\text{-}3\text{-piperidyl})\text{methyl}\}\text{-}1\text{-}$   
 $\{(2\text{S},4\text{R})\text{-}4\text{-hydroxy-}1\text{-}(3,3,3\text{-triphenylpropanoyl})\text{pyrrolidin-}2\text{-yl}\}\text{-}$   
 $\text{carbonylpyrrolidine-}2\text{-carboxamide}$

The title compound was prepared by a method similar to Step 3 of Example 17, using  $(2\text{R})\text{-}1\text{-}\{((2\text{S},4\text{R})\text{-}4\text{-hydroxy-}1\text{-}(3,3,3\text{-triphenylpropanoyl})\text{pyrrolidin-}2\text{-yl})\text{carbonyl-N-}\{((3\text{R})\text{-}3\text{-piperidyl-methyl})\text{pyrrolidine-}2\text{-carboxamide}$  and cyclohexyl methyl ketone. The compound was obtained as a white solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.80\text{-}2.08(27\text{H}, \text{m}), 2.22\text{-}3.15$   
 $(7\text{H}, \text{m}), 3.32\text{-}3.46(2\text{H}, \text{m}), 3.58\text{-}3.77(1\text{H}, \text{m}), 3.84\text{-}3.93$   
 $(2\text{H}, \text{m}), 4.28\text{-}4.40(2\text{H}, \text{m}), 4.52\text{-}4.60(1\text{H}, \text{m}), 7.18\text{-}7.40$   
 $(16\text{H}, \text{m})$

ESI-MS( $m/e$ , as  $(\text{C}_{45}\text{H}_{58}\text{N}_4\text{O}_4+\text{H})^+$ ): 719

#### Example 120

$(2\text{R})\text{-N-}\{((3\text{S})\text{-}1\text{-cyclohexyl-}3\text{-piperidyl})\text{methyl}\}\text{-}1\text{-}$   
 $\{(2\text{S},4\text{R})\text{-}4\text{-hydroxy-}1\text{-}(3,3,3\text{-triphenylpropanoyl})\text{pyrrolidin-}2\text{-yl}\}\text{-}$   
 $\text{carbonylpyrrolidine-}2\text{-carboxamide}$

The title compound was prepared by a method similar to Example 119, using cyclopentanone. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.70-2.08(21H, m), 2.26-2.35  
(1H, m), 2.39-2.53(2H, m), 2.79-3.03(3H, m), 3.04-3.18  
(1H, m), 3.30-3.40(1H, m), 3.42(1H, d, J=14.5Hz), 3.58  
(1H, dd, J=4.0, 10.9Hz), 3.79-3.90(1H, m), 3.89  
5 (1H, d, J=14.5Hz), 4.30-4.40(2H, m), 4.54-4.60(1H, m),  
7.16-7.38(16H, m)  
ESI-MS(m/e, as (C<sub>42</sub>H<sub>52</sub>N<sub>4</sub>O<sub>4</sub>+H)<sup>+</sup>): 677

#### Example 121

10 (2R)-N-(4-piperidylmethyl)-1-((2S)-1-{3,3,3-tris(4-  
fluorophenyl)propanoyl}pyrrolidin-2-yl)carbonylpyrrolidine-2-  
carboxamide

The title compound was prepared by a method similar to  
Example 64, using 3,3,3-tris(4-fluorophenyl)propionic acid. The  
15 compound was obtained as a white foamy substance.

<sup>10</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.88-1.10(2H, m), 1.44-1.70  
(4H, m), 1.75-2.09(7H, m), 2.30-2.40(1H, m), 2.48-2.60  
(3H, m), 2.92-3.13(4H, m), 3.31-3.48(2H, m), 3.42  
(1H, d, J=14.8Hz), 3.76(1H, d, J=14.8Hz), 3.78-3.84  
20 (1H, m), 4.21(1H, t, J=6.9Hz), 4.59-4.64(1H, m), 6.97  
(6H, dd, J<sub>HF</sub>=8.8Hz, J<sub>HH</sub>=8.8Hz), 7.08-7.26(1H, m), 7.18  
(6H, dd, J<sub>HF</sub>=5.2Hz, J<sub>HH</sub>=8.8Hz)  
ESI-MS(m/e, as (C<sub>37</sub>H<sub>41</sub>F<sub>3</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 647

#### 25 Example 122

(2R)-N-{(1-methyl-4-piperidyl)methyl}-1-((2S)-1-{3,3,3-  
tris(4-fluorophenyl)propanoyl}pyrrolidin-2-yl)carbonylpyrrolidine-2-  
carboxamide

The title compound was prepared by a method similar to  
30 Example 95, using (2R)-N-(4-piperidylmethyl)-1-((2S)-1-{3,3,3-tris-

(4-fluorophenyl)propanoyl}pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 1.12-1.33(3H, m), 1.35-1.50  
(1H, m), 1.52-1.70(3H, m), 1.77-2.08(7H, m), 2.29(3H, s),  
5 2.30-2.39(1H, m), 2.60-2.71(1H, m), 2.80-2.90(2H, m),  
2.91-3.10(2H, m), 3.31-3.50(2H, m), 3.41(1H, d, J=14.9Hz),  
3.77(1H, d, J=14.9Hz), 3.78-3.85(1H, m), 4.20(1H, t, J=6.9Hz),  
4.58-4.63(1H, m), 6.97(6H, dd, J<sub>HF</sub>=8.9Hz, J<sub>HH</sub>=8.9Hz),  
7.08-7.23(1H, m), 7.19(6H, dd, J<sub>HF</sub>=5.2Hz, J<sub>HH</sub>=8.9Hz)  
10 ESI-MS(m/e, as (C<sub>38</sub>H<sub>43</sub>F<sub>3</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 661

### Example 123

(2R)-N-{(1-ethyl-4-piperidyl)methyl}-1-((2S)-1-{3,3,3-tris-  
(4-fluorophenyl)propanoyl}pyrrolidin-2-yl)carbonylpyrrolidine-2-  
15 carboamide

The title compound was prepared by a method similar to  
Example 93, using (2R)-N-(4-piperidylmethyl)-1-((2S)-1-{3,3,3-tris-  
(4-fluorophenyl)propanoyl}pyrrolidin-2-yl)carbonylpyrrolidine-2-  
carboxamide. The compound was obtained as a white foamy  
20 substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 1.09(3H, t, J=7.1Hz), 1.15-1.33  
(3H, m), 1.34-1.50(1H, m), 1.52-1.68(3H, m), 1.74-2.08  
(7H, m), 2.29-2.35(1H, m), 2.40(2H, q, J=7.1Hz), 2.60-2.70  
(1H, m), 2.87-2.98(3H, m), 2.99-3.10(1H, m), 3.30-3.50(2H, m),  
25 3.39(1H, d, J=14.8Hz), 3.76(1H, d, J=14.8Hz), 3.77-3.83  
(1H, m), 4.19(1H, t, J=6.9Hz), 4.58-4.62(1H, m), 6.95  
(6H, dd, J<sub>HF</sub>=8.8Hz, J<sub>HH</sub>=8.8Hz), 7.06-7.12(1H, m), 7.17  
(6H, dd, J<sub>HF</sub>=5.3Hz, J<sub>HH</sub>=8.8Hz)  
ESI-MS(m/e, as (C<sub>39</sub>H<sub>45</sub>F<sub>3</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 675

30



Example 124

(2R)-N-((1-propyl-4-piperidyl)methyl)-1-((2S)-1-{3,3,3-tris-(4-fluorophenyl)propanoyl}pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide

5           The title compound was prepared by a method similar to Example 122, using propionaldehyde. The product was obtained as a white foamy substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.90(3H, t, J=7.3Hz),  
1.03-2.10(16H, m), 2.22-2.38(3H, m), 2.59-2.70(1H, m),  
10       2.85-2.99(3H, m), 3.00-3.10(1H, m), 3.30-3.50(2H, m),  
3.40(1H, d, J=14.9Hz), 3.77(1H, d, J=14.9Hz), 3.78-3.84  
(1H, m), 4.20(1H, t, J=6.9Hz), 4.57-4.62(1H, m), 6.95  
(6H, dd, J<sub>HF</sub>=8.9Hz, J<sub>HH</sub>=8.9Hz), 7.06-7.15(1H, m), 7.18  
(6H, dd, J<sub>HF</sub>=5.2Hz, J<sub>HH</sub>=8.9Hz)

15           ESI-MS(m/e, as (C<sub>40</sub>H<sub>47</sub>F<sub>3</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 689

Example 125

(2R)-N-((1-cyclopropylmethyl-4-piperidyl)methyl)-1-((2S)-1-{3,3,3-tris(4-fluorophenyl)propanoyl}pyrrolidin-2-yl)carbonyl-  
20 pyrrolidine-2-carboxamide

The title compound was prepared by a method similar to Example 122, using cyclopropanecarbaldehyde. The product was obtained as a white foamy substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.08-0.14(2H, m), 0.48-0.56  
25       (2H, m), 0.83-2.10(15H, m), 2.20-2.28(2H, m), 2.30-2.39  
(1H, m), 2.62-2.72(1H, m), 2.89-2.97(1H, m), 2.99-3.11(3H, m),  
3.30-3.50(2H, m), 3.41(1H, d, J=14.9Hz), 3.77(1H, d,  
J=14.9Hz), 3.78-3.86(1H, m), 4.20(1H, t, J=6.9Hz),  
4.58-4.63(1H, m), 6.96(6H, dd, J<sub>HF</sub>=8.8Hz, J<sub>HH</sub>=8.8Hz),  
30       7.03-7.12(1H, m), 7.18(6H, dd, J<sub>HF</sub>=5.3Hz, J<sub>HH</sub>=8.8Hz)

ESI-MS(m/e, as (C<sub>41</sub>H<sub>47</sub>F<sub>3</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 701

Example 126

N-{3-((3S)-3-piperidylmethyl)amino-3-oxopropyl}-1-(3,3,3-triphenylpropanoyl)-2-pyrrolidinecarboxamide

5           The title compound was obtained by successively conducting procedures similar to Steps 1-5 of Example 1 and Step 2 of Example 17, using tert-butoxycarbonyl-L-proline. The compound was obtained as a white foamy substance.

10           <sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.95-1.98(11H, m), 2.06-2.12 (1H, m), 2.18-2.28(2H, m), 2.44-2.56(1H, m), 2.83-3.10 (4H, m), 3.18-3.32(1H, m), 3.33-3.54(2H, m), 3.63 (1H, d, J=15.3Hz), 3.77(1H, d, J=15.3Hz), 4.12-4.20(1H, m), 6.32-6.41(1H, m), 6.63-6.71(1H, m), 7.12-7.30(15H, m)  
ESI-MS(m/e, as (C<sub>35</sub>H<sub>42</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 567

15

Example 127

N-{3-(((3R)-1-(cyclohexylmethyl)-3-piperidyl)methylamino)-3-oxopropyl}-1-(3,3,3-triphenylpropanoyl)-2-pyrrolidinecarboxamide

20           The title compound was prepared by a method similar to Example 12, using N-{3-((3S)-3-piperidylmethyl)amino-3-oxopropyl}-1-(3,3,3-triphenylpropanoyl)-2-pyrrolidinecarboxamide. The compound was obtained as a white foamy substance.

25           <sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.78-2.22(27H, m), 2.62-3.18 (4H, m), 3.20-3.58(3H, m), 3.64(1H, d, J=15.2Hz), 3.77 (1H, d, J=15.2Hz), 4.13-4.20(1H, m), 6.28-6.40(1H, m), 6.60-6.70(1H, m), 7.16-7.32(15H, m)  
ESI-MS(m/e, as (C<sub>42</sub>H<sub>54</sub>N<sub>4</sub>O<sub>3</sub>+H)<sup>+</sup>): 663

Example 128

30           (3S)-3-((((2R)-1-(((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-

propanoyl)-2-pyrrolidinyl}carbonyl)-2-pyrrolidinyl}carbonyl)amino}-  
methyl)-1,1-dimethylpiperidinium bromide

To 15 mg of (2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-  
propanoyl)pyrrolidin-2-yl}carbonyl-N-(((3S)-1-methyl-3-piperidyl)-  
5 methyl}pyrrolidine-2-carboxamide, 0.5 ml of 10% methyl bromide-  
acetonitrile was added at room temperature, followed by 12 hours'  
stirring. The solvent in the reaction liquid was distilled off under  
reduced pressure, and the resulting residue was purified by  
preparative thin-layer chromatography (aluminium oxide 60F<sub>254</sub>, Art.  
10 5713 (Merck), chloroform/methanol = 18/1) to provide 15 mg of the title  
compound as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.86-2.30(12H, m), 2.62-3.80  
(17H, m), 3.87-3.98(1H, m), 4.36-4.48(1H, m), 4.49-4.62  
(2H, m), 7.10-7.36(15H, m), 7.42-7.54(1H, m)

15 ESI-MS(m/e, as (C<sub>39</sub>H<sub>49</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 637

#### Example 129

(3S)-1,1-diethyl-3-((((2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-  
triphenylpropanoyl)-2-pyrrolidinyl}carbonyl)-2-pyrrolidinyl}-  
20 carbonyl)amino)methyl)piperidinium chloride

To 22 mg of (2R)-N-(((3S)-1-ethyl-3-piperidyl)methyl)-1-  
{(2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}-  
carbonylpyrrolidine-2-carboxamide, 1 ml of ethyl iodide was added at  
room temperature, followed by 2 hours' stirring at 70°C. The  
25 resultant reaction liquid was diluted with chloroform and the solvent  
was distilled off under reduced pressure. The resultant residue was  
dissolved in ultrapure water 0.6 ml/methanol 0.1 ml and the solution  
was developed on reversed phase medium-pressure liquid

chromatography [ODS-AQ 120-S50 (YMC)]. Purification and anion exchange were conducted by pouring 20 ml of saturated brine, washing with 150 ml of ultrapure water and eluting the title compound with methanol/water = 1/1, to provide 21 mg of the title compound as a white solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.82\text{-}2.30(18\text{H}, \text{m}), 2.50\text{-}3.88(16\text{H}, \text{m}), 4.37\text{-}4.52(3\text{H}, \text{m}), 7.13\text{-}7.36(15\text{H}, \text{m}), 7.57\text{-}7.64(1\text{H}, \text{m})$

ESI-MS( $m/e$ , as  $(\text{C}_{41}\text{H}_{53}\text{N}_4\text{O}_4)^+$ ): 665

#### Example 130

(3S)-3-((((2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)carbonyl)-amino)methyl)-1,1-dipropylpiperidinium iodide

To 4.9 mg of (2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-N-(((3S)-1-propyl-3-piperidyl)methyl)pyrrolidine-2-carboxamide, 1 ml of propyl iodide was added at room temperature, followed by 15 hours' stirring at 100°C under heating. The reaction liquid was diluted with chloroform, the solvent was distilled off under reduced pressure, and the resulting residue was purified with preparative thin-layer chromatography (aluminium oxide 60F<sub>254</sub>, Art 5713 (Merck), chloroform/methanol = 18/1) to provide 4.1 mg of the title compound as a pale yellow solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.84\text{-}0.92(1\text{H}, \text{m}), 1.01(3\text{H}, \text{t}, J=7.1\text{Hz}), 1.06(3\text{H}, \text{t}, J=7.1\text{Hz}), 1.16\text{-}1.37(3\text{H}, \text{m}), 1.52\text{-}2.12(11\text{H}, \text{m}), 2.18\text{-}2.39(2\text{H}, \text{m}), 2.77\text{-}2.93(3\text{H}, \text{m}), 3.08\text{-}3.33(3\text{H}, \text{m}), 3.35\text{-}3.73(6\text{H}, \text{m}), 3.50(1\text{H}, \text{d}, J=14.8\text{Hz}), 3.82\text{-}3.90(1\text{H}, \text{m}), 3.94(1\text{H}, \text{d}, J=14.8\text{Hz}), 4.31\text{-}4.40(2\text{H}, \text{m}), 4.45\text{-}4.60(1\text{H}, \text{m}), 7.15\text{-}7.40(15\text{H}, \text{m}), 7.58\text{-}7.66(1\text{H}, \text{m})$

ESI-MS( $m/e$ , as  $(\text{C}_{43}\text{H}_{57}\text{N}_4\text{O}_4)^+$ ): 693

Example 131

(3S)-1,1-dicyclopropylmethyl-3-((((2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)carbonyl)amino)methyl)piperidinium bromide

5           The title compound was prepared by a method similar to Example 130, using (2R)-N-(((3S)-1-cyclopropylmethyl-3-piperidyl)-methyl)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonylpyrrolidine-2-carboxamide and cyclopropylmethyl bromide. The compound was obtained as a white solid.

10           <sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.68-1.77(18H, m), 1.80-2.20 (4H, m), 2.22-2.36(1H, m), 2.64-2.78(1H, m), 2.90-3.10(2H, m), 3.30-3.70(8H, m), 3.52(1H, d, J=14.8Hz), 3.72-4.01(2H, m), 3.88(1H, d, J=14.8Hz), 4.36-4.60(3H, m), 7.16-7.43(15H, m), 7.49-7.70(1H, m)

15           ESI-MS(m/e, as (C<sub>45</sub>H<sub>57</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 717

Example 132

(3R)-3-((((2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)carbonyl)amino)-methyl)-1,1-dimethylpiperidinium bromide

20

          The title compound was prepared by a method similar to Example 128, using (2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonyl-N-(((3R)-1-methyl-3-piperidyl)-methyl)pyrrolidine-2-carboxamide. The compound was obtained as a

25   white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.83-2.07(9H, m), 2.12-2.34(3H, m), 2.48-2.70(2H, m), 2.86-3.01(2H, m), 3.10-3.47(8H, m), 3.50-3.80(2H, m), 3.55(1H, d, J=14.8Hz), 3.71(1H, d, J=14.8Hz), 3.96-4.12(2H, m), 4.30-4.40(1H, m), 4.55-4.62(1H,

m), 4.67-4.76(1H, m), 7.10-7.38(15H, m), 7.58-7.68(1H, m)  
FAB-MS(m/e, as (C<sub>39</sub>H<sub>49</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 637

#### Example 133

5        (3R)-1,1-diethyl-3-((((2R)-1-(((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-2-pyrrolidinyl}carbonyl)-2-pyrrolidinyl}carbonyl)-amino)methyl)piperidinium chloride

The title compound was prepared by a method similar to Example 129, using (2R)-N-(((3R)-1-ethyl-3-piperidyl)methyl)-1-  
10    {(2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}-carbonylpyrrolidine-2-carboxamide. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.89-1.46(10H, m), 1.68-2.10  
(6H, m), 2.20-2.30(2H, m), 2.34-2.50(2H, m), 3.05-3.90  
15    (12H, m), 3.60(1H, d, J=15.7Hz), 3.71(1H, d, J=15.7Hz), 4.37-4.45(1H, m), 4.52-4.67(2H, m), 7.13-7.40(15H, m), 7.58-7.69(1H, m)

FAB-MS(m/e, as (C<sub>41</sub>H<sub>53</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 665

#### 20    Example 134

(3R)-1,1-diallyl-3-((((2R)-1-(((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-2-pyrrolidinyl}carbonyl)-2-pyrrolidinyl}carbonyl)-amino)methyl)piperidinium bromide

The title compound was prepared by a method similar to  
25    Example 128, using (2R)-N-(((3R)-1-allyl-3-piperidyl)methyl)-1-{{(2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonyl}-pyrrolidine-2-carboxamide and allyl bromide. The compound was obtained as a white foamy substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.80-2.28(13H, m), 2.52-2.65

(1H, m), 2.66-2.78(1H, m), 2.78-2.96(1H, m), 3.00-3.12  
 (1H, m), 3.20-3.49(4H, m), 3.50(1H, d, J=14.3Hz), 3.72  
 (1H, d, J=14.3Hz), 3.76-3.86(1H, m), 3.88-4.07(3H, m),  
 4.18-4.30(1H, m), 4.30-4.42(2H, m), 4.50-4.60(2H, m),  
 5.70-5.78(2H, m), 5.79-5.88(1H, m), 5.90-6.10(2H, m),  
 7.16-7.38(15H, m), 7.62-7.70(1H, m)  
 FAB-MS(m/e, as (C<sub>43</sub>H<sub>53</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 689

### Example 135

(3R)-3-((((2R)-1-(((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-  
 propanoyl)-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)carbonyl)amino}-  
 methyl)-1,1-dipropylpiperidinium chloride

The title compound was prepared by a method similar to  
 Example 129, using (2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-  
 propanoyl)pyrrolidin-2-yl)carbonyl-N-(((3R)-1-propyl-3-piperidyl)-  
 methyl)pyrrolidine-2-carboxamide and propyl iodide. The compound  
 was obtained as a pale yellow solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.80-2.10(19H, m), 2.15-2.32  
 (2H, m), 2.48-2.60(2H, m), 2.90-3.00(2H, m), 3.01-3.59(9H, m),  
 3.53(1H, d, J=14.6Hz), 3.63-3.80(1H, m), 3.75  
 (1H, d, J=14.6Hz), 3.88-3.98(1H, m), 4.30-4.38(1H, m),  
 4.55-4.70(2H, m), 7.15-7.43(15H, m), 7.67-7.77(1H, m)  
 ESI-MS(m/e, as (C<sub>43</sub>H<sub>57</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 693

### Example 136

(3R)-1-butyl-3-((((2R)-1-(((2S,4R)-4-hydroxy-1-(3,3,3-triphen-  
 ylpropanoyl)-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)carbonyl)-  
 amino)methyl)-1-methylpiperidinium bromide

The title compound was prepared by a method similar to  
 Example 128, using (2R)-N-(((3R)-1-butyl-3-piperidyl)methyl)-1-

{(2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}-  
carbonylpyrrolidine-2-carboxamide and (bromomethyl)cyclopropane.  
The compound was obtained as a white foamy substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.82-2.17(15H, m), 2.18-2.39  
5 (3H, m), 2.72-2.84(2H, m), 2.85-3.12(3H, m), 3.13-3.78  
(9H, m), 3.52(1H, d, J=14.4Hz), 3.71(1H, d, J=14.4Hz),  
3.83-4.06(2H, m), 4.32-4.40(1H, m), 4.49-4.82(2H, m),  
7.16-7.40(15H, m), 7.56-7.75(1H, m)  
FAB-MS(m/e, as (C<sub>42</sub>H<sub>55</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 679

10

### Example 137

(3R)-3-((((2R)-1-(((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-  
propanoyl)-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)carbonyl)amino)-  
methyl)-1-methyl-1-(2-methylbutyl)piperidinium bromide

15

The title compound was prepared by a method similar to  
Example 128, using (2R)-1-(((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-  
propanoyl)pyrrolidin-2-yl)carbonyl-N-((((3R)-1-(2-methylbutyl)-3-  
piperidyl)methyl)pyrrolidine-2-carboxamide). The compound was  
obtained as a white solid.

20

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.70-2.20(18H, m), 2.22-2.50  
(2H, m), 2.78-3.05(4H, m), 3.06-3.80(10H, m), 3.53  
(1H, d, J=14.1Hz), 3.69(1H, d, J=14.1Hz), 3.83-3.95(1H, m),  
4.08-4.23(1H, m), 4.32-4.80(3H, m), 7.10-7.47(15H, m),  
7.48-7.80(1H, m)

25

FAB-MS(m/e, as (C<sub>43</sub>H<sub>57</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 693

### Example 138

(1R\*,3R)- and (1S\*,3R)- 3-((((2R)-1-(((2S,4R)-4-hydroxy-1-  
(3,3,3-triphenylpropanoyl)-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-

30



carbonyl)amino)methyl)-1-methyl-1-pentylpiperidinium bromide

After conducting a procedure similar to Example 128, using (2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-N-(((3R)-1-pentyl-3-piperidyl)methyl)pyrrolidine-2-carboxamide, the resulting diastereomer was separated, to provide the title compound which was expediently named (1R\*)-form as a low-polarity substance in the form of a white solid, and the title compound expediently named (1S\*)-form, as a high-polarity substance in the form of a white solid.

(1R\*)-form

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.86-1.21(4H, m), 1.28-1.47(4H, m), 1.50-2.17(13H, m), 2.20-2.37(2H, m), 2.68-2.78(1H, m), 2.88-3.03(2H, m), 3.04-3.20(1H, m), 3.25(3H, s), 3.34-3.68(4H, m), 3.51(1H, d, J=14.1Hz), 3.73(1H, d, J=14.1Hz), 3.98-4.08(2H, m), 4.28-4.40(1H, m), 4.50-4.61(2H, m), 7.18-7.40(15H, m), 7.58-7.65(1H, m)  
FAB-MS(m/e, as (C<sub>43</sub>H<sub>57</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 693

(1S\*)-form

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.88-1.08(4H, m), 1.28-1.42(4H, m), 1.43-2.02(10H, m), 2.08-2.37(4H, m), 2.97-3.10(2H, m), 3.15(3H, s), 3.16-3.63(7H, m), 3.58(1H, d, J=15.5Hz), 3.71(1H, d, J=15.5Hz), 3.84-3.92(1H, m), 3.92-4.03(1H, m), 4.38-4.42(1H, m), 4.58-4.63(1H, m), 4.76(1H, t, J=8.3Hz), 7.15-7.39(15H, m), 7.66-7.73(1H, m)  
FAB-MS(m/e, as (C<sub>43</sub>H<sub>57</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 693

Example 139

(1R\*,3R)- and (1S\*,3R)-3-((((2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-carbonyl)amino)methyl)-1-methyl-1-octylpiperidinium bromide

After conducting a procedure similar to Example 128, using (2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)-carbonyl-N-(((3R)-1-octyl-3-piperidyl)methyl)pyrrolidine-2-carboxamide, the resulting diastereomer was separated, to provide the title compound which was expediently named (1R\*)-form as a low-polarity substance in the form of a white foamy substance, and the title compound expediently named (1S\*)-form, as a high-polarity substance in the form of a white solid.

(1R\*)-form

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.87(3H, t, J=6.7Hz), 0.98-2.38(26H, m), 2.73-2.98(3H, m), 3.02-3.14(1H, m), 3.22(3H, s), 3.37-3.62(4H, m), 3.52(1H, d, J=14.2Hz), 3.72(1H, d, J=14.2Hz), 3.93-4.08(2H, m), 4.30-4.38(1H, m), 4.50-4.60(2H, m), 7.18-7.40(15H, m), 7.58-7.65(1H, m)  
FAB-MS(m/e, as (C<sub>46</sub>H<sub>63</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 735

(1S\*)-form

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.87(3H, t, J=6.7Hz), 0.92-1.10(1H, m), 1.18-2.05(21H, m), 2.10-2.40(4H, m), 2.75-3.60(8H, m), 3.15(3H, s), 3.58(1H, d, J=15.4Hz), 3.72(1H, d, J=15.4Hz), 3.79-3.90(1H, m), 3.93-4.06(1H, m), 4.34-4.45(1H, m), 4.49-4.82(2H, m), 7.15-7.38(15H, m), 7.56-7.75(1H, m)  
FAB-MS(m/e, as (C<sub>46</sub>H<sub>63</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 735

Example 140

(3R)-1,1-dicyclopropylmethyl-3-((((2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)carbonyl)amino)methyl)piperidinium bromide

The title compound was prepared by a method similar to Example 131, using (2R)-N-(((3R)-1-cyclopropylmethyl-3-piperidyl)-

methyl}-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl pyrrolidine-2-carboxamide. The compound was obtained as a white foamy substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.54-0.70(3H, m), 0.73-0.85(2H, m),  
5 0.88(4H, t, J=6.6Hz), 1.00-2.25(13H, m), 2.47-2.60(1H, m),  
2.70-2.84(2H, m), 2.92-3.10(2H, m), 3.38-3.75(8H, m),  
3.78-3.98(3H, m), 4.20-4.40(1H, m), 4.40-4.50(1H, m),  
4.52-4.58(1H, m), 7.16-7.42(15H, m), 7.83-7.91(1H, m)  
FAB-MS(m/e, as (C<sub>45</sub>H<sub>57</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 717

10

#### Example 141

(1R\*,3R)- and (1S\*,3R)-1-cyclohexylmethyl-3-(((2R)-1-  
(((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-2-pyrrolidinyl)carbo-  
nyl)-2-pyrrolidinyl)-carbonyl)amino)methyl-1-methylpiperidinium  
15 bromide

After conducting a procedure similar to Example 128 using  
(2R)-N-(((3R)-1-cyclohexylmethyl-3-piperidyl)methyl)-1-((2S,4R)-4-  
hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-  
pyrrolidine-2-carboxamide, the resulting diastereomer was separated,  
20 to provide the title compound which was expediently named  
(1R\*)-form as a low polarity substance in the form of a white solid,  
and the title compound expediently named (1S\*)-form, as a  
high-polarity substance in the form of a white solid.

#### (1R\*)-form

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 1.02-2.23(21H, m), 2.30-2.40  
25 (1H, m), 2.67-2.78(1H, m), 2.83-3.02(3H, m), 3.20-3.37  
(5H, m), 3.38-3.65(5H, m), 3.56(1H, d, J=14.4Hz), 3.70  
(1H, d, J=14.4Hz), 3.84-4.02(1H, m), 4.10-4.19(1H, m),  
4.30-4.38(1H, m), 4.40-4.49(2H, m), 7.15-7.40(15H, m),  
30 7.50-7.60(1H, m)

FAB-MS(m/e, as (C<sub>45</sub>H<sub>59</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 719

(1S\*)-form

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.80-2.07(18H, m), 2.18-2.38  
(4H, m), 2.72-3.36(10H, m), 3.38-3.50(4H, m), 3.56  
(1H, d, J=14.9Hz), 3.73(1H, d, J=14.9Hz), 3.76-3.85(1H, m),  
5 4.02-4.12(1H, m), 4.33-4.40(1H, m), 4.60(1H, d, J=6.6Hz),  
4.77(1H, t, J=8.1Hz), 7.12-7.40(15H, m), 7.77(1H, t, J=5.7Hz)  
FAB-MS(m/e, as (C<sub>45</sub>H<sub>59</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 719

#### Example 142

10 (3R)-1-cycloheptylmethyl-3-(((2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-carbonyl)amino)methyl)-1-methylpiperidinium bromide

The title compound was prepared by a method similar to  
Example 128, using (2R)-N-(((3R)-1-cycloheptylmethyl-3-  
15 piperidyl)methyl)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide. The compound  
was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.83-1.35(6H, m), 1.36-2.02  
(14H, m), 2.03-2.21(3H, m), 2.22-2.64(2H, m), 2.80-3.00  
20 (4H, m), 3.08-3.30(5H, m), 3.31-3.74(4H, m), 3.54  
(1H, d, J=14.5Hz), 3.68(1H, d, J=14.5Hz), 3.82-3.95(1H, m),  
4.09-4.18(1H, m), 4.33-4.78(3H, m), 7.10-7.39(15H, m),  
7.47-7.72(1H, m)  
FAB-MS(m/e, as (C<sub>46</sub>H<sub>61</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 733

25

#### Example 143

(3R)-1,1-diethyl-3-(((2R)-1-((2S,3R,4S)-3,4-dihydroxy-1-(3,3,3-triphenylpropanoyl)-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-carbonyl)amino)methyl)piperidinium chloride

30 The title compound was prepared by a method similar to  
Example 129, using (2R)-N-(((3R)-1-ethyl-3-piperidyl)methyl)-1-

{(2S,3R,4S)-3,4-dihydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl}carbonylpyrrolidine-2-carboxamide. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.85-2.40(16H, m), 2.92-3.78  
5 (16H, m), 4.18-4.35(3H, m), 4.43-4.58(2H, m), 7.10-7.35  
(15H, m), 7.48-7.65(1H, m)  
FAB-MS(m/e, as (C<sub>41</sub>H<sub>53</sub>N<sub>4</sub>O<sub>5</sub>)<sup>+</sup>): 681

#### Example 144

10 (3R)-1,1-diethyl-3-((((2R)-1-(((2S,4R)-4-hydroxy-1-{3,3,3-tris-(4-chlorophenyl)propanoyl}-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-carbonyl)amino)methyl)piperidinium chloride

The title compound was prepared by a method similar to Example 129, using (2R)-N-(((3R)-1-ethyl-3-piperidyl)methyl)-1-  
15 (((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-chlorophenyl)propanoyl}pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide). The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 1.26(6H, t, J=7.1Hz),  
1.32-2.19(11H, m), 2.20-2.35(2H, m), 2.38-2.49(1H, m),  
20 3.17-3.85(12H, m), 3.92-4.03(1H, m), 4.16-4.30(1H, m),  
4.39-4.44(1H, m), 4.56-4.60(1H, m), 4.72-4.81(1H, m),  
7.06-7.18(6H, m), 7.20-7.30(6H, m), 7.60-7.67(1H, m)  
ESI-MS(m/e, as (C<sub>41</sub>H<sub>50</sub>Cl<sub>3</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 767

#### 25 Example 145

(3R)-1,1-diethyl-3-((((2R)-1-(((2S,4R)-4-hydroxy-1-{3,3,3-tris-(4-ethylphenyl)propanoyl}-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-carbonyl)amino)methyl)piperidinium chloride

The title compound was prepared by a method similar to

Example 129, using (2R)-N-(((3R)-1-ethyl-3-piperidyl)methyl)-1-((2S,4R)-4-hydroxy-1-{3,3,3-tris(4-ethylphenyl)propanoyl}pyrrolidin-2-yl)carbonylpyrrolidine-2-carboxamide. The compound was obtained as a white solid.

5  $^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.82\text{-}1.20(3\text{H}, \text{m}), 1.22$   
(9H, t,  $J=7.5\text{Hz}$ ),  $1.30\text{-}2.55(17\text{H}, \text{m}), 2.61(6\text{H}, \text{q}, J=7.5\text{Hz}),$   
 $2.74\text{-}4.30(14\text{H}, \text{m}), 4.32\text{-}4.46(1\text{H}, \text{m}), 4.47\text{-}4.56(2\text{H}, \text{m}),$   
 $7.01\text{-}7.22(12\text{H}, \text{m}), 7.50\text{-}7.75(1\text{H}, \text{m})$   
ESI-MS( $m/e$ , as  $(\text{C}_{47}\text{H}_{65}\text{N}_4\text{O}_4)^+$ ): 749

10

Example 146

(3R)-1-heptyl-1-methyl-3-(((3-{(2-{(3,3,3-triphenylpropanoyl)-  
amino}acetyl)amino}propanoyl)amino)methyl)piperidinium bromide

The title compound was prepared by a method similar to  
15 Example 128, using N-{2-(3-(((3R)-1-heptyl-3-piperidyl)methyl)amino-3-oxopropyl)amino-2-oxoethyl}-3,3,3-triphenylpropanamide. The compound was obtained as a white solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.80\text{-}2.60(20\text{H}, \text{m}), 2.82\text{-}3.82$   
(17H, m),  $6.62\text{-}6.88(1\text{H}, \text{m}), 7.09\text{-}7.40(16\text{H}, \text{m}),$   
20  $7.85\text{-}7.99(1\text{H}, \text{m})$   
FAB-MS( $m/e$ , as  $(\text{C}_{40}\text{H}_{55}\text{N}_4\text{O}_3)^+$ ): 639

Example 147

(3R)-1-heptyl-1-methyl-3-(((3-{(2-{(3,3,3-triphenylpropanoyl)-  
25 (methyl)amino}acetyl)amino}propanoyl)amino)methyl)piperidinium  
bromide

The title compound was prepared by a method similar to  
Example 128, using N-{2-(3-(((3R)-1-heptyl-3-piperidyl)methyl)amino-3-oxopropyl)amino-2-oxoethyl}-N-methyl-3,3,3-triphenylpropanamide.

30

The compound was obtained as a white solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.80\text{-}2.32(20\text{H}, \text{m}), 2.45\text{-}4.05$   
 $(20\text{H}, \text{m}), 6.88\text{-}8.13(17\text{H}, \text{m})$

FAB-MS( $m/e$ , as  $(\text{C}_{41}\text{H}_{57}\text{N}_4\text{O}_3)^+$ ): 653

5

#### Example 148

1-Cyclooctylmethyl-1-ethyl-3-(((6-((3,3,3-triphenylpropanoyl)-  
amino)hexanoyl)amino)methyl)piperidinium iodide

The title compound was prepared by a method similar to  
10 Example 130, using N-(6-((1-cyclooctylmethyl-3-piperidyl)methyl)-  
amino-6-oxohexyl)-3,3,3-triphenylpropanamide and ethyl iodide.  
The compound was obtained as a pale yellow solid.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta\text{ppm}): 1.00\text{-}2.27(31\text{H}, \text{m}), 2.78\text{-}2.97$   
 $(3\text{H}, \text{m}), 3.02\text{-}3.54(9\text{H}, \text{m}), 3.60(2\text{H}, \text{s}), 7.12\text{-}7.30(15\text{H}, \text{m})$

15

FAB-MS( $m/e$ , as  $(\text{C}_{44}\text{H}_{62}\text{N}_3\text{O}_2)^+$ ): 664

#### Example 149

(3S)-1-ethyl-1-((2S)-2-methylbutyl)-3-(((6-((3,3,3-triphenyl-  
propanoyl)amino)hexanoyl)amino)methyl)piperidinium iodide

20 (Step 1)

Synthesis of N-{6-(((3S)-1-((2S)-2-methylbutyl)-3-piperidyl)-  
methyl)amino-6-oxohexyl)-3,3,3-triphenylpropanamide

The title compound was prepared by a method similar to  
Example 77, using (3S)-3-aminomethyl-1-(t-butoxycarbonyl)-  
25 piperidine and (2S)-2-methylbutane iodide. The compound was  
obtained as a white solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.86\text{-}0.92(6\text{H}, \text{m}), 0.98\text{-}1.18$   
 $(6\text{H}, \text{m}), 1.37\text{-}1.73(7\text{H}, \text{m}), 1.82\text{-}2.00(2\text{H}, \text{m}), 2.18$   
 $(2\text{H}, \text{t}, J=7.4\text{Hz}), 2.20\text{-}2.28(3\text{H}, \text{m}), 2.68\text{-}2.80(2\text{H}, \text{m}), 2.91$

30

(2H, dd, J=6.0, 12.5Hz), 3.09-3.28(2H, m), 3.56(2H, s),  
4.80-4.88(1H, m), 5.78-5.88(1H, m), 7.17-7.32(15H, m)  
FAB-MS(m/e, as (C<sub>38</sub>H<sub>51</sub>N<sub>3</sub>O<sub>2</sub>+H)<sup>+</sup>): 582

(Step 2)

5                    Synthesis of (3S)-1-ethyl-1-((2S)-2-methylbutyl)-3-(((6-  
    {((3,3,3-triphenylpropanoyl)amino)hexanoyl)amino)methyl)-  
piperidinium iodide

                    The title compound was prepared by a method similar to  
Example 148, using N-{6-(((3S)-1-((2S)-2-methylbutyl)-3-piperidyl)-  
10 methyl)amino-6-oxohexyl)-3,3,3-triphenylpropanamide. The title  
compound was obtained as a yellow oily substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.98(3H, t, J=7.4Hz),  
                    1.01-1.78(15H, m), 1.80-2.10(3H, m), 2.27(2H, t, J=7.5Hz),  
                    2.42-2.58(1H, m), 2.89(2H, dd, J=5.9, 12.0Hz), 3.02-3.70  
15                    (10H, m), 3.56(2H, s), 3.76-3.90(1H, m), 5.03-5.12(1H, m),  
                    7.17-7.35(15H, m), 7.50-7.60(1H, m)  
                    FAB-MS(m/e, as (C<sub>40</sub>H<sub>56</sub>N<sub>3</sub>O<sub>2</sub>)<sup>+</sup>): 610

Example 150

20                    (3S)-1-ethyl-1-((2S)-2-methylbutyl)-3-(((6-((3,3,3-triphenyl-  
    propanoyl)amino)hexanoyl)amino)methyl)piperidinium chloride

(Step 1)

                    Synthesis of N-(6-(((3S)-1-ethyl-3-piperidyl)methyl)amino-6-  
oxohexyl)-3,3,3-triphenylpropanamide

25                    The title compound was prepared by a method similar to  
Example 27, using (3S)-3-aminomethyl-1-(t-butoxycarbonyl)-  
piperidine and acetaldehyde. The compound was obtained as a white  
solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.90-1.16(8H, m), 1.43-1.80(7H, m),  
30                    1.90(1H, t, J=10.8Hz), 2.06(2H, t, J=7.4Hz), 2.38



(2H, q, J=7.1Hz), 2.77-2.85(2H, m), 2.86-2.96(2H, m),  
3.10-3.20(2H, m), 3.56(2H, s), 4.80-4.90(1H, m), 5.62-5.72  
(1H, m), 7.17-7.32(15H, m)

FAB-MS(m/e, as (C<sub>35</sub>H<sub>45</sub>N<sub>3</sub>O<sub>2</sub>+H)<sup>+</sup>): 540

5 (Step 2)

Synthesis of (3S)-1-ethyl-1-((2S)-2-methylbutyl)-3-  
(((6-((3,3,3-triphenylpropanoyl)amino)hexanoyl)amino)methyl)-  
piperidinium chloride

The title compound was prepared by a method similar to  
10 Example 129, using N-(6-(((3S)-1-ethyl-3-piperidyl)methyl)amino-  
6-oxohexyl)-3,3,3-triphenylpropanamide and (2S)-2-methylbutane  
iodide. The compound was obtained as a white foamy substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.86-1.73(18H, m), 1.80-2.10  
(3H, m), 2.20-2.37(2H, m), 2.39-2.56(1H, m), 2.87-2.95(2H, m),  
15 3.08-3.70(10H, m), 3.56(2H, s), 3.87-4.05(1H, m),  
5.18-5.28(1H, m), 7.14-7.38(15H, m), 8.40-8.58(1H, m)

FAB-MS(m/e, as (C<sub>40</sub>H<sub>56</sub>N<sub>3</sub>O<sub>2</sub>)<sup>+</sup>): 610

Example 151

20 (7R)-7-((((2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-  
propanoyl)-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)carbonyl)amino)-  
methyl)-5-azoniaspiro [4.5]decane chloride

The method of Japan Kokai (laid-open) No. Sho 62(1987)-  
215588 A1 was followed. In 0.6 ml of chloroform, 41 mg of (2R)-1-  
25 ((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)-  
carbonyl-N-((3S)-3-piperidylmethyl)pyrrolidine-2-carboxamide, 0.014  
ml of diethylamine and 0.032 ml of 1,4-dibromobutane were dissolved,  
and the solution was allowed to stand in a hermetically sealed vessel  
for 6 days. The reaction liquid was diluted with chloroform and the  
30 solvent was distilled off under reduced pressure. The resultant

residue was dissolved in a mixture of ultrapure water 0.6 ml/methanol 0.1 ml, and developed on a reversed phase medium pressure liquid chromatography [ODS-AQ 120-S50 (YMC)]. The product was purified and anion-exchanged by pouring 20 ml of saturated brine, washing with 150 ml of ultrapure water, and eluting from methanol/water = 1/1, to provide 45 mg of the title compound as a white solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm})$ : 0.88(2H, t,  $J=6.8\text{Hz}$ ), 0.98-1.18 (1H, m), 1.21-1.34(3H, m), 1.65-2.38(12H, m), 2.52-2.68 (1H, m), 2.98-3.17(3H, m), 3.20-3.60(5H, m), 3.56 (1H, d,  $J=14.4\text{Hz}$ ), 3.70(1H, d,  $J=14.4\text{Hz}$ ), 3.79-3.95(2H, m), 3.96-4.04(1H, m), 4.37-4.41(1H, m), 4.51-4.60(2H, m), 7.17-7.39(15H, m), 7.56(1H, t,  $J=6.0\text{Hz}$ )  
FAB-MS( $m/e$ , as  $(\text{C}_{41}\text{H}_{51}\text{N}_4\text{O}_4)^+$ ): 663

#### Example 152

(7R)-7-((((2R)-1-(((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)carbonyl)amino)-methyl)-5-azoniaspiro [4.5]dec-2-en chloride

The title compound was prepared by a method similar to Example 151, using 1,4-dibromo-2-butene which was synthesized following the method of M. A. Keegstra, et al. [*Syn. Commun.* Vol. 21, 721-726 (1991)]. The compound was obtained as a white solid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm})$ : 0.80-2.80(15H, m), 2.99-4.62 (16H, m), 5.80-6.00(2H, m), 7.15-7.68(16H, m)  
ESI-MS( $m/e$ , as  $(\text{C}_{41}\text{H}_{49}\text{N}_4\text{O}_4)^+$ ): 661

#### Example 153

(2R)-2-((((2R)-1-(((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-

propanoyl)-2-pyrrolidinyl}carbonyl)-2-pyrrolidinyl}carbonyl)amino}-  
methyl)-6-azoniaspiro [5.5] undecane chloride

The title compound was prepared by a method similar to  
Example 151, using 1,5-dibromopentane. The compound was  
5 obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.88(2H, t, J=6.6Hz), 0.98-1.13  
(1H, m), 1.20-1.36(3H, m), 1.68-2.07(10H, m), 2.08-2.32  
(3H, m), 2.40-2.52(1H, m), 2.80-2.95(1H, m), 3.04-3.20(2H, m),  
3.22-3.80(7H, m), 3.57(1H, d, J=15.3Hz), 3.68  
10 (1H, d, J=15.3Hz), 3.88-3.96(1H, m), 4.07-4.16  
(1H, m), 4.38-4.43(1H, m), 4.56-4.68(2H, m), 7.17-7.39  
(15H, m), 7.64(1H, t, J=6.5Hz)  
FAB-MS(m/e, as (C<sub>42</sub>H<sub>53</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 677

15 Example 154

(2R)-2-((((2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-  
propanoyl)-2-pyrrolidinyl}carbonyl)-2-pyrrolidinyl}carbonyl)amino)-  
methyl)-9,9-dimethyl-6-azoniaspiro [5.5] undecane chloride

The title compound was prepared by a method similar to  
20 Example 151, using 1,5-dibromo-3,3-dimethylpentane. The  
compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.80-2.33(18H, m), 1.09(3H, s),  
1.24(3H, s), 2.60-3.92(12H, m), 3.52(1H, d, J=14.5Hz),  
3.68(1H, d, J=14.5Hz), 4.26-4.56(3H, m), 7.15-7.66(16H, m)  
25 FAB-MS(m/e, as (C<sub>44</sub>H<sub>57</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 705

Example 155

(8R)-8-((((2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-  
propanoyl)-2-pyrrolidinyl}carbonyl)-2-pyrrolidinyl}carbonyl)amino)-  
30 methyl)-3-oxa-6-azoniaspiro [5.5] undecane chloride

The title compound was prepared by a method similar to Example 151, using 2,2'-dichlorodiethyl ether. The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.80-2.78(17H, m), 2.95-4.51  
5 (18H, m), 7.12-7.78(16H, m)  
ESI-MS(m/e, as (C<sub>41</sub>H<sub>51</sub>N<sub>4</sub>O<sub>5</sub>)<sup>+</sup>): 679

#### Example 156

(7R)-2,3-epoxy-7-((((2R)-1-(((2S,4R)-4-hydroxy-1-(3,3,3-  
10 triphenylpropanoyl)-2-pyrrolidinyl}carbonyl)-2-pyrrolidinyl}carbonyl)-  
amino}methyl)-5-azoniaspiro [4.5] decane chloride

The title compound was prepared by a method similar to Example 151, using 1,4-dibromo-2,3-epoxybutane (cf. Referential Example 10). The compound was obtained as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.80-2.50(17H, m), 2.60-4.85  
15 (16H, m), 7.10-7.45(15H, m), 7.58-7.80(1H, m)  
ESI-MS(m/e, as (C<sub>41</sub>H<sub>49</sub>N<sub>4</sub>O<sub>5</sub>)<sup>+</sup>): 677

#### Example 157

3-((((2R)-1-(((2S,4R)-4-hydroxy-1-(3,3,3-triphenylpropanoyl)-  
20 2-pyrrolidinyl}carbonyl)-2-pyrrolidinyl}carbonyl)amino}methyl)-1,1-  
dimethylpyrrolidinium bromide

(Step 1)

Synthesis of (2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-  
25 propanoyl)pyrrolidin-2-yl}carbonyl-N-(3-pyrrolidylmethyl)pyrrolidine-  
2-carboxamide

The title compound was prepared by successively conducting procedures similar to Step 5 of Example 1 and Example 46, using 3-aminomethyl-1-(t-butoxycarbonyl)pyrrolidine [which was synthesized

by a method similar to the one described in Japan Kokai Hei  
11(1999)-193232, using 3-hydroxymethyl-1-benzylpyrrolidine [taught  
in Japan Kokai (laid-open) Hei 4(1992)-112868]] and (2R)-1-((2S,4R)-  
4-(tert-butoxy)-1-(3,3,3-triphenylpropanoyl)pyrrolidin-2-yl)carbonyl-p  
5 yrrolidine-2-carboxylic acid.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.80\text{-}2.34(9\text{H}, \text{m}), 2.49\text{-}2.64(1\text{H}, \text{m}),$   
 $2.67\text{-}2.81(1\text{H}, \text{m}), 2.82\text{-}3.29(7\text{H}, \text{m}), 3.30\text{-}3.42(1\text{H}, \text{m}),$   
 $3.43\text{-}3.65(2\text{H}, \text{m}), 3.70\text{-}3.90(2\text{H}, \text{m}), 4.29\text{-}4.43(2\text{H}, \text{m}),$   
 $4.49\text{-}4.61(1\text{H}, \text{m}), 7.13\text{-}7.57(16\text{H}, \text{m})$

10 ESI-MS(m/e, as  $(\text{C}_{36}\text{H}_{42}\text{N}_4\text{O}_4+\text{H})^+$ ): 595

(Step 2)

Synthesis of (2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-  
propanoyl)pyrrolidin-2-yl)carbonyl-N-((1-methyl-3-pyrrolidyl)methyl)-  
pyrrolidine-2-carboxamide

15 The title compound was prepared by a method similar to  
Example 48, using (2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-  
propanoyl)pyrrolidin-2-yl)carbonyl-N-(3-pyrrolidylmethyl)pyrrolidine-  
2-carboxamide.

$^1\text{H-NMR}(\text{CDCl}_3, \delta\text{ppm}): 0.83\text{-}2.12(9\text{H}, \text{m}), 2.20\text{-}2.46(3\text{H}, \text{m}),$   
20  $2.31(3\text{H}, \text{s}), 2.49\text{-}2.83(4\text{H}, \text{m}), 3.10\text{-}3.27(1\text{H}, \text{m}), 3.29\text{-}3.40$   
 $(1\text{H}, \text{m}), 3.42(1\text{H}, \text{d}, J=14.5\text{Hz}), 3.56\text{-}3.62(1\text{H}, \text{m}),$   
 $3.77\text{-}3.85(1\text{H}, \text{m}), 3.87(1\text{H}, \text{d}, J=14.5\text{Hz}), 4.30\text{-}4.39(2\text{H}, \text{m}),$   
 $4.52\text{-}4.59(1\text{H}, \text{m}), 7.15\text{-}7.39(16\text{H}, \text{m})$

ESI-MS(m/e, as  $(\text{C}_{37}\text{H}_{44}\text{N}_4\text{O}_4+\text{H})^+$ ): 609

25 (Step 3)

Synthesis of 3-((((2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-  
triphenylpropanoyl)-2-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-  
carbonyl)amino)methyl)-1,1-dimethylpyrrolidinium bromide

The title compound was prepared by a method similar to  
30 Example 130, using (2R)-1-((2S,4R)-4-hydroxy-1-(3,3,3-triphenyl-

propanoyl)pyrrolidin-2-yl}carbonyl-N-((1-methyl-3-pyrrolidyl)methyl)-pyrrolidine-2-carboxamide. The compound was obtained as a colorless oily substance.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δppm): 0.82-2.35(9H, m), 2.52-2.70(1H, m),  
5 2.72-2.89(1H, m), 3.00-3.89(18H, m), 4.25-4.60(2H, m),  
7.10-7.40(15H, m), 7.48-7.78(1H, m)  
ESI-MS(m/e, as (C<sub>38</sub>H<sub>47</sub>N<sub>4</sub>O<sub>4</sub>)<sup>+</sup>): 623

#### Referential Example 1

10 (3R)-3-aminomethyl-1-(tert-butoxycarbonyl)piperidine  
(Step 1)

Synthesis of ethyl (3S)-3-piperidinecarboxylate

To 13.0 g of ethyl (3S)-3-piperidinecarboxylate D(-)-  
tartarate which was synthesized following the method of P. Magnus,  
15 et al. [J. Org. Chem. Vol. 56, 1166-1170 (1991)], 3N aqueous sodium  
hydroxide solution was added to render the former basic, followed by  
extraction with chloroform and drying over anhydrous magnesium  
sulfate. Distilling the solvent off under reduced pressure, 7.50 g of  
the title compound was obtained.

20 (Step 2)

Synthesis of (3S)-3-piperidylmethanol

~~To solution~~ To a solution of 7.50 g of ethyl  
(3S)-3-piperidinecarboxylate in 200 ml of tetrahydrofuran, 3.4 g of  
lithium aluminium ~~hydrate~~ hydride was added under cooling with ice,  
25 followed by an hour's refluxing under heating. To the reaction liquid  
sodium sulfate ~~decahydrate~~ decahydride was added under cooling  
with ice, followed by 12 hours' stirring at room temperature and  
filtration through cerite. Distilling the filtrate off under reduced  
pressure, 5.89 g of the title compound was obtained.

30 (Step 3)

Synthesis of {(3S)-1-(tert-butoxycarbonyl)-3-piperidyl}-  
methanol

To a solution of 5.89 g of (3S)-3-piperidylmethanol in 150 ml of chloroform, another solution of 9.3 g of di-tert-butyl dicarbonate in  
5 50 ml of chloroform was added under cooling with ice, followed by 15 hours' stirring at room temperature. The reaction liquid was distilled off under reduced pressure, diluted with diethyl ether, washed successively with 0.5 N hydrochloric acid, water and saturated brine, and dried over anhydrous magnesium sulfate.  
10 Distilling the solvent off under reduced pressure, 8.01 g of the title compound was obtained.

(Step 4)

Synthesis of {(3S)-1-(tert-butoxycarbonyl)-3-piperidyl}-  
methyl methanesulfonate

15 To a solution of 7.96 g of {(3S)-1-(tert-butoxycarbonyl)-3-piperidyl}methanol in 150 ml of chloroform, 3.4 ml of methanesulfonyl chloride and 6.7 ml of triethylamine were added under cooling with ice, followed by an hour's stirring at room temperature. The reaction liquid was distilled off under reduced pressure, diluted with ethyl  
20 acetate and saturated aqueous sodium bicarbonate solution was added, followed by 1.5 hours' stirring. Thereafter the reaction liquid was successively washed with water and saturated brine and dried over anhydrous magnesium sulfate. Distilling the solvent off, 10.50 g of the title compound was obtained.

25 (Step 5)

Synthesis of (3S)-3-azidomethyl-1-(tert-butoxycarbonyl)-  
piperidine

To a solution of ~~10.50 g of~~ 10.50 g of  
{(3S)-1-(tert-butoxycarbonyl)-3-  
30 piperidyl}methyl methanesulfonate in 100 ml of N,N-dimethylform-

amide, 4.9 g of sodium azide was added at room temperature, followed by 4 hours' stirring at 80°C under heating. The reaction liquid was diluted with ethyl acetate, washed successively with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and resulting residue was purified by means of silica gel column chromatography (eluting solvent: from hexane to hexane/ethyl acetate = 15/1) to provide 7.24 g of the title compound.

(Step 6)

10            Synthesis of (3R)-3-aminomethyl-1-(tert-butoxycarbonyl)-piperidine

To a solution of 600 mg of (3S)-3-azidomethyl-1-(tert-butoxycarbonyl)piperidine in 12.5 ml of 20% hydrous tetrahydrofuran, 622 mg of triphenylphosphine was added at room temperature, followed by 45 minutes' refluxing under heating. The reaction liquid was rendered acidic by addition of 0.5 N hydrochloric acid, and successively washed with chloroform and ethyl acetate. Then 4N aqueous sodium hydroxide solution was added to the aqueous layer to render the latter basic, followed by extraction with chloroform and drying over anhydrous sodium sulfate. Distilling the solvent off under reduced pressure, 497 mg of the title compound was obtained.

Referential Example 2

(3R)-3-aminomethyl-1-(cyclohexylmethyl)piperidine

25    (Step 1)

Synthesis of ((3S)-1-cyclohexylmethyl-3-piperidyl)methanol

To a solution of 900 mg of (3S)-3-piperidylmethanol in 60 ml of tetrahydrofuran, 1.05 g of cyclohexanecarbaldehyde, 0.54 ml of acetic acid and 2.5 g of sodium triacetoxymethylborohydride were successively added at room temperature by the order stated, followed by 21 hours' stirring at the same



temperature. The reaction liquid was rendered acidic with 1N hydrochloric acid and washed with

chloroform. The aqueous layer was rendered basic with 4N aqueous sodium hydroxide solution, followed by extraction with chloroform and drying over anhydrous sodium sulfate. Distilling the solvent off under reduced pressure, 990 mg of the title compound was obtained.

(Step 2)

Synthesis of (3R)-3-aminomethyl-1-(cyclohexylmethyl)-piperidine

The title compound was prepared by procedures similar to Steps 4-6 of Referential Example 1, using ((3S)-1-cyclohexylmethyl-3-piperidyl)methanol.

Referential Example 3

(3S)-3-aminomethyl-1-(tert-butoxycarbonyl)piperidine

The title compound was prepared by a method similar to Referential Example 1, using ethyl (3R)-3-piperidinecarboxylate L<sup>(+)</sup>-tartarate which was synthesized following the method of P. Magnus, et al. [J. Org. Chem., Vol. 56, pp. 1166-1170 (1991)].

Referential Example 4

3-Aminomethyl-1-(tert-butoxycarbonyl)piperidine

The title compound was prepared by procedures similar to Steps 2-6 of Referential Example 1, using ethyl 3-piperidine-carboxylate.

Referential Example 5

3-Aminomethyl-1-(cyclohexylmethyl)piperidine

The title compound was prepared by successively conducting procedures similar to Step 2 of Referential Example 1 and Referential Example 2, using ethyl 3-piperidinecarboxylate.

5    Referential Example 6

3,3,3-Tris(4-fluorophenyl)propionic acid

The synthesis was conducted referring to the method of Fan Benlun, et al. [Yiyao Gongye, Vol. 9, pp. 2-4 (1983)]. In 1.1 ml of acetic acid, 1.0 g of 3,3,3-tris (4-fluorophenyl) methanol was  
10    suspended. To the suspension 541 mg of cyanoacetic acid and 230 mg of zinc chloride were added at room temperature, followed by 4 hours' stirring at 130°C under heating. The reaction liquid was cooled to room temperature, and 1.8 ml of conc. sulfuric acid and 0.64 ml of acetic anhydride were added, followed by 17 hours' stirring at  
15    130°C under heating. The reaction liquid was cooled to room temperature, diluted with water and filtered. The filter cake was thoroughly washed with ~~waterto~~ water to provide 940 mg of the title compound.

20    Referential Example 7

Cyclopentylmethyl methanesulfonate

The title compound was synthesized by a method similar to Step 4 of Referential Example 1, using cyclopentylmethanol.

25    Referential Example 8

2-(1-Methylcyclopropan-1-yl)acetaldehyde

(Step 1)

Synthesis of 1-methylcyclopropane-1-carbaldehyde

To a solution of 0.5 ml of 2-cyclopropanepropanol in 6 ml of

dimethyl sulfoxide, 3 ml of triethylamine and a solution of 2.5 g of sulfur trioxide-pyridine complex in 4 ml of dimethyl sulfoxide were successively added at room temperature, followed by 4.5 hours' stirring at the same temperature. The reaction solution was poured into water, extracted with diethyl ether, and the organic layer was washed with water and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, about 10 ml of a diethyl ether solution of the title compound was obtained.

(Step 2)

10                    Synthesis of 2-(1-methylcyclopropan-1-yl)acetaldehyde

                  Methoxymethyltriphenylphosphonium chloride 2.57 g was suspended in 40 ml of diethyl ether, and to the suspension n-butyl lithium (1.47 M hexane solution, 8.0 ml) was added under cooling with ice, followed by 2 hours' stirring at room temperature. Then 10 ml of a diethyl ether solution of 1-methylcyclopropane-1-carbaldehyde was added at room temperature, followed by an hour's stirring at the same temperature. The reaction solution was poured into water, extracted with diethyl ether, and the organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off under slightly reduced pressure, and the resultant residue was dissolved in 10 ml of tetrahydrofuran. To the solution 10 ml of conc. hydrochloric acid and 5 ml of water were added at room temperature, followed by 12 hours' stirring at the same temperature. The reaction solution was poured into water, extracted with diethyl ether, and the organic layer was washed with water and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, about 15 ml of a diethyl ether solution of the title compound was obtained.

30    Referential Example 9

1-(Cyclopentyl)ethyl 4-methylbenzenesulfonate

To 0.9 ml of a pyridine solution of 1-cyclopentaneethanol, 309 mg of 4-methylbenzenesulfonyl chloride was added under cooling with ice, followed by 6.5 hours' stirring at room temperature. A hydrochloric acid solution was added under cooling with ice to render  
5 the reaction liquid acidic, followed by extraction with ethyl acetate. The organic solvent layer was washed with saturated brine and dried over anhydrous sodium sulfate. Distilling the solvent off under reduced pressure, 324 mg of the title compound was obtained.

#### 10 Referential Example 10

##### Preparation of 1,4-dibromo-2,3-epoxybutane

To a solution of 500 mg of 1,4-dibromo-2-butene in 1 ml of chloroform, 485 mg of meta-chloroperbenzoic acid was added under cooling with ice, followed by 20 hours' stirring at room temperature.  
15 Further 606 mg of meta-chloroperbenzoic acid was added, followed by 3 days' stirring. The reaction liquid was then poured into a mixed aqueous solution of sodium hydrogencarbonate and sodium thiosulfate, extracted with chloroform and dried over anhydrous sodium sulfate. Distilling the solvent off under reduced pressure,  
20 512 mg of the title compound was obtained.

#### Industrial Applicability

Because ~~these compounds~~ those compounds of the present invention exhibit selective antagonism to muscarinic  $M_3$  receptors,  
25 they are useful as safe and effective treating agents of diseases of the respiratory, urinary or digestive systems, exhibiting little side effect.